

What is claimed is:

1. A method for treating or preventing a
5 neoplasia disorder in a mammal in need of such treatment
or prevention, which method comprises administering to
said mammal a therapeutically-effective amount of a
combination of a cyclooxygenase-2 inhibitor, an integrin
10 antagonist, and an antineoplastic agent, wherein said
antineoplastic agent is selected from the group
consisting of anastrozole, calcium carbonate,
capecitabine, carboplatin, cisplatin, Cell Pathways CP-
461, docetaxel, doxorubicin, etoposide, fluorouracil (5-
FU), fluoxymestrine, gemcitabine, goserelin, irinotecan,
15 ketoconazole, letrozol, leucovorin, levamisole,
megestrol, mitoxantrone, paclitaxel, raloxifene,
retinoic acid, tamoxifen, thiotepa, topotecan,
toremifene, vinorelbine, vinblastine, vincristine,
selenium (selenomethionine), ursodeoxycholic acid,
20 sulindac sulfone, exemestane and eflornithine (DFMO).

2. The method of Claim 1 wherein the combination
is administered in a sequential manner.

25 3. The method of Claim 1 wherein the combination
is administered in a substantially simultaneous manner.

4. The method of Claim 1 wherein the
antineoplastic agent is capecitabine.

5. The method of Claim 1 wherein the antineoplastic agent is carboplatin.

6. The method of Claim 1 wherein the
5 antineoplastic agent is cisplatin.

7. The method of Claim 1 wherein the antineoplastic agent is Cell Pathways CP-461.

10 8. The method of Claim 1 wherein the antineoplastic agent is docetaxel.

9. The method of Claim 1 wherein the antineoplastic agent is doxorubicin.

15 10. The method of Claim 1 wherein the antineoplastic agent is etoposide.

11. The method of Claim 1 wherein the
20 antineoplastic agent is fluoxymestrine.

12. The method of Claim 1 wherein the antineoplastic agent is gemcitabine.

25 13. The method of Claim 1 wherein the antineoplastic agent is goserelin.

14. The method of Claim 1 wherein the antineoplastic agent is irinotecan.

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15. The method of Claim 1 wherein the antineoplastic agent is ketoconazole.

16. The method of Claim 1 wherein the
5 antineoplastic agent is letrozol.

17. The method of Claim 1 wherein the antineoplastic agent is leucovorin.

10 18. The method of Claim 1 wherein the antineoplastic agent is levamisole.

19. The method of Claim 1 wherein the antineoplastic agent is megestrol.

15 20. The method of Claim 1 wherein the antineoplastic agent is mitoxantrone.

20 21. The method of Claim 1 wherein the antineoplastic agent is paclitaxel.

22. The method of Claim 1 wherein the antineoplastic agent is raloxifene.

25 23. The method of Claim 1 wherein the antineoplastic agent is retinoic acid.

24. The method of Claim 1 wherein the antineoplastic agent is tamoxifen.

30

25. The method of Claim 1 wherein the antineoplastic agent is thiotepa.

26. The method of Claim 1 wherein the
5 antineoplastic agent is topotecan.

27. The method of Claim 1 wherein the antineoplastic agent is toremifene.

10 28. The method of Claim 1 wherein the antineoplastic agent is vinorelbine.

29. The method of Claim 1 wherein the antineoplastic agent is vinblastine.

15 30. The method of Claim 1 wherein the antineoplastic agent is vincristine.

31. The method of Claim 1 wherein the
20 antineoplastic agent is selenium (selenomethionine).

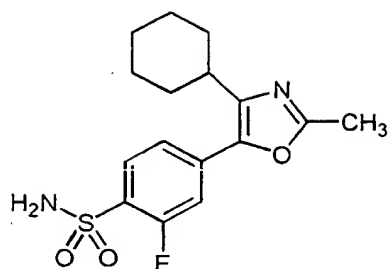
32. The method of Claim 1 wherein the antineoplastic agent is sulindac sulfone.

25 33. The method of Claim 1 wherein the antineoplastic agent is eflornithine (DFMO).

34. The method of Claim 1 wherein the cyclooxygenase-2 inhibitor is selected from compounds,
30 and their pharmaceutically acceptable salts thereof, of the group consisting of:

-221-

1)



JTE-522, 4-(4-cyclohexyl-2-methyloxazol-5-yl)-
2-fluorobenzenesulfonamide,

5

2)

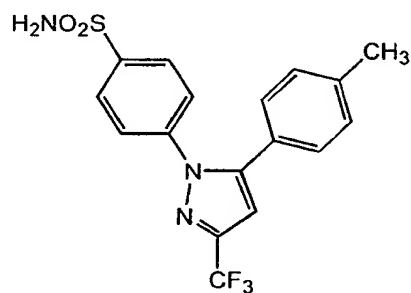
5-chloro-3-(4-(methylsulfonyl)phenyl)-2-
(methyl-5-pyridinyl)pyridine,

3)

2-(3,5-difluorophenyl)-3-4-
(methylsulfonyl)phenyl)-2-cyclopenten-1-one,

10

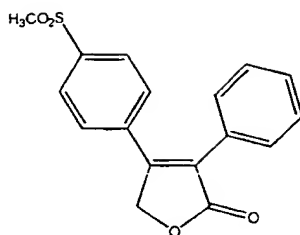
4)



4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-
pyrazol-1-yl]-benzenesulfonamide,

-222-

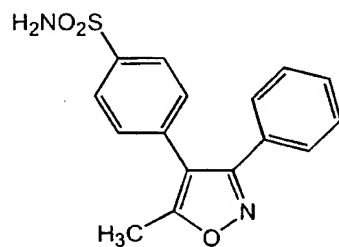
5)



rofecoxib, 4-(4-(methylsulfonyl)phenyl)-3-phenyl-2(5H)-furanone,

5

6)

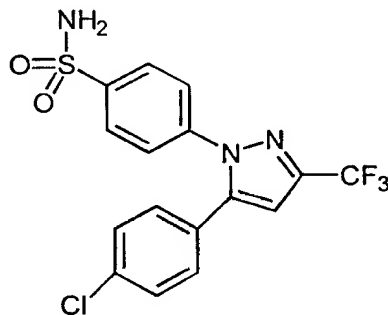


4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide,

7) N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide,

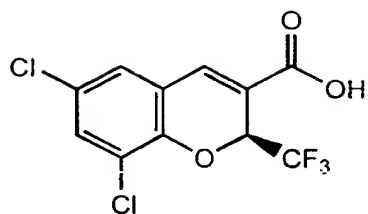
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8)

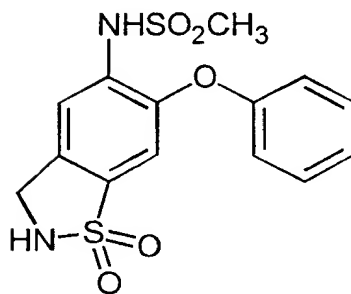


4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl]benzenesulfonamide,

9)

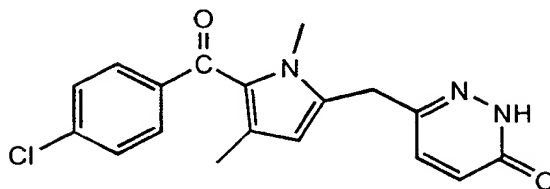


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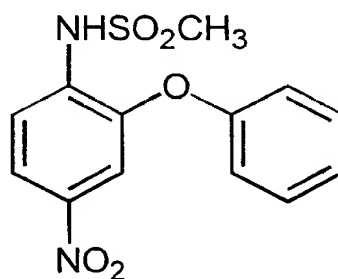
5

11)



6-[[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone,

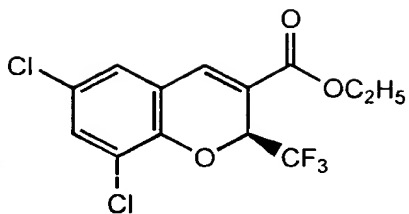
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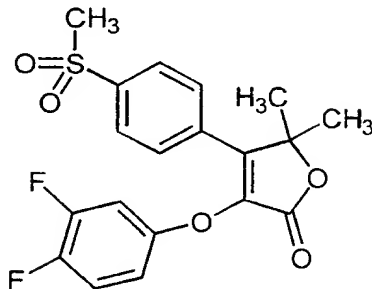
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N-(4-nitro-2-phenoxyphenyl)methanesulfonamide,

13)



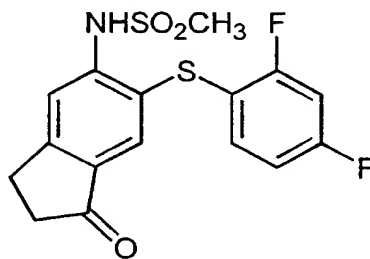
14)



5

3-(3,4-difluorophenoxy)-5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-2(5H)-furanone,

15)

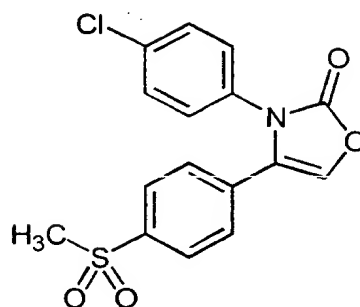


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N-[6-[(2,4-difluorophenyl)thio]-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide,

-225-

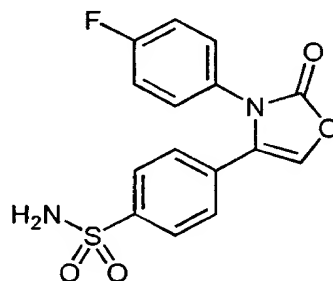
16)



3-(4-chlorophenyl)-4-[4-(methanesulfonyl)phenyl]-2(3H)-oxazolone,

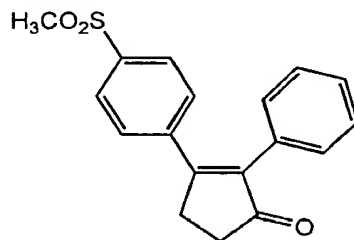
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17)



4-[3-(4-fluorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide,

18)

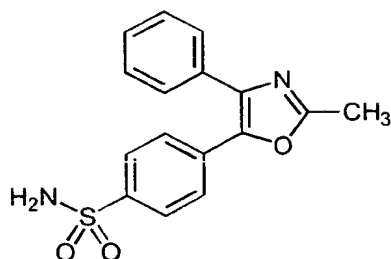


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3-[4-(methanesulfonyl)phenyl]-2-phenyl-2-cyclopenten-1-one,

-226-

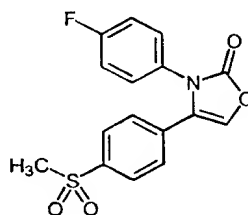
19)



4-(2-methyl-4-phenyl-5-oxazolyl)benzenesulfonamide,

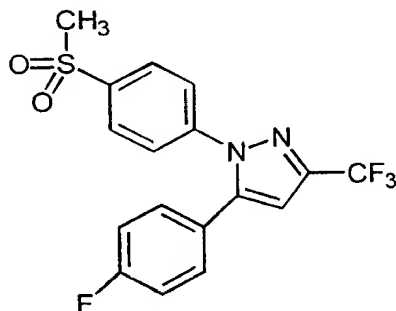
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20)



3-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2(3H)-oxazolone,

21)

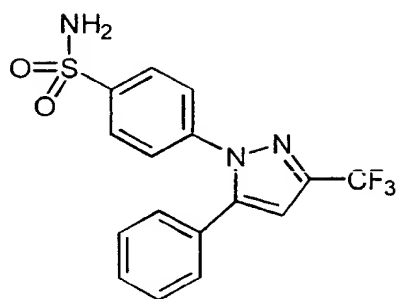


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5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole,

-227-

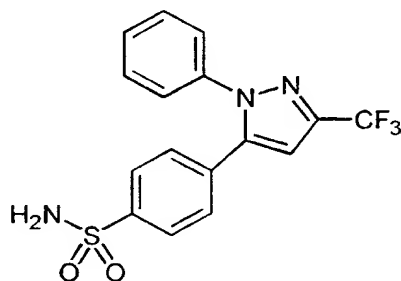
22)



4-[5-phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,

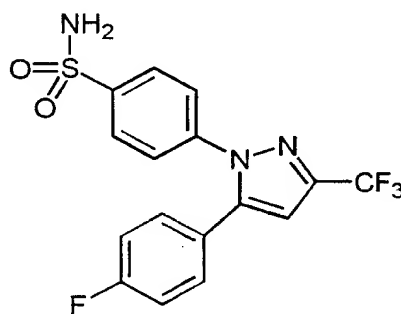
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23)



4-[1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide,

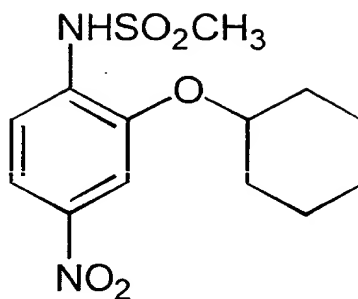
24)



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4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,

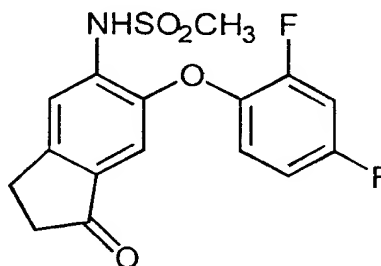
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N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide,

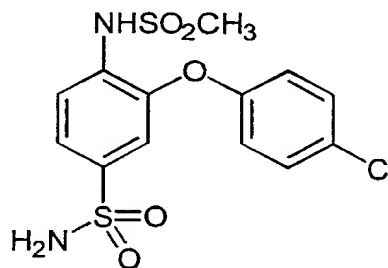
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26)



N-[6-(2,4-difluorophenoxy)-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide,

27)

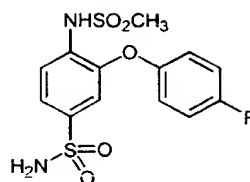


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3-(4-chlorophenoxy)-4-[(methanesulfonyl)amino]benzenesulfonamide,

-229-

28)

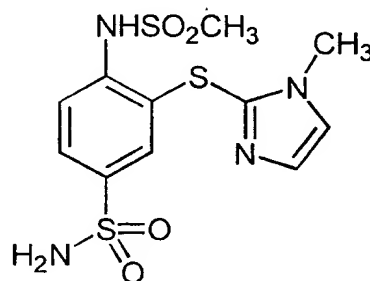


3-(4-fluorophenoxy)-4-

[(methylsulfonyl)amino]benzenesulfonamide,

5

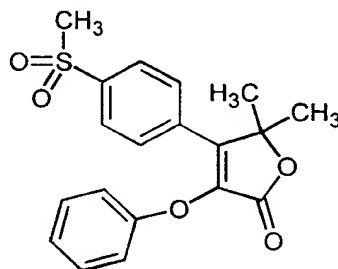
29)



3-[(1-methyl-1H-imidazol-2-yl)thio]-4

[(methylsulfonyl) amino]benzenesulfonamide,

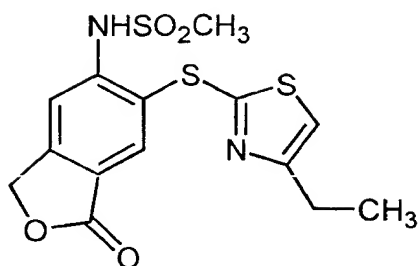
30)



10

5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-3-
phenoxy-2(5H)-furanone,

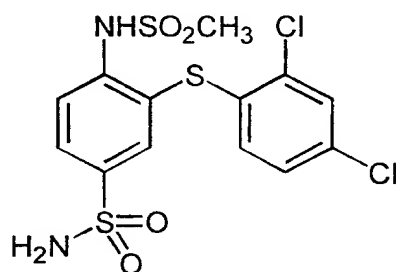
31)



N-[6-[(4-ethyl-2-thiazolyl)thio]-1,3-dihydro-1-oxo-5-isobenzofuranyl]methanesulfonamide,

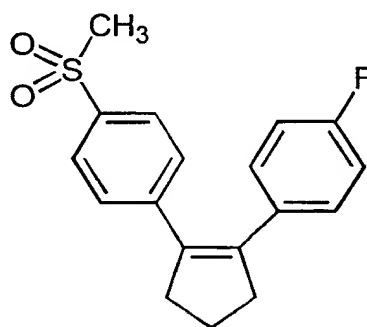
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32)



3-[(2,4-dichlorophenyl)thio]-4-[(methanesulfonyl)amino]benzenesulfonamide,

33)

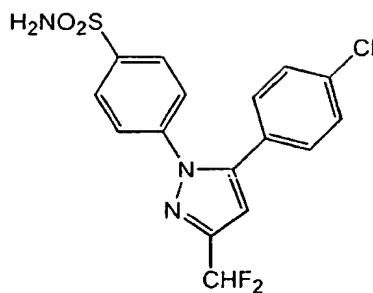


10

1-fluoro-4-[2-[4-(methanesulfonyl)phenyl]cyclopenten-1-yl]benzene,

-231-

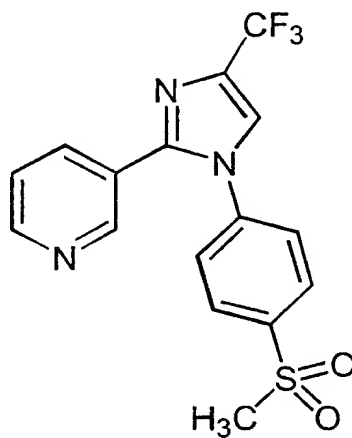
34)



4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,

5

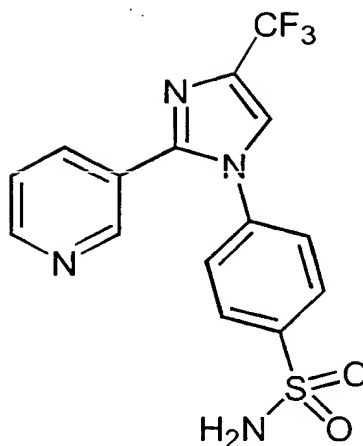
35)



3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine,

-232-

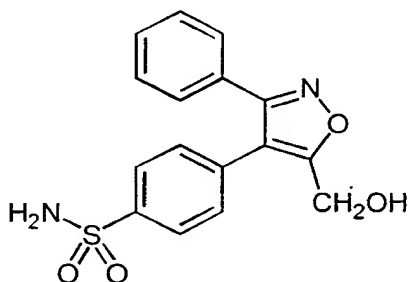
36)



4-[2-(3-pyridinyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide,

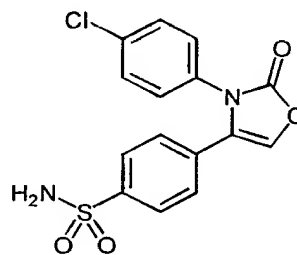
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37)



4-[5-(hydroxymethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide,

38)

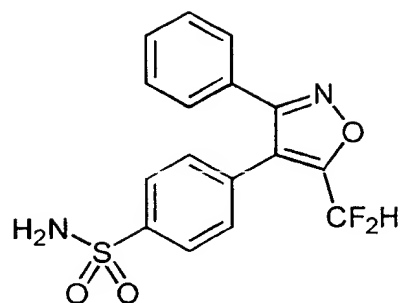


10

4-[3-(4-chlorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide,

-233-

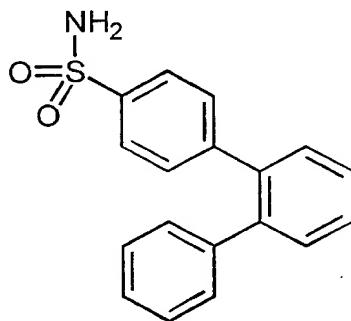
39)



4-[5-(difluoromethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide,

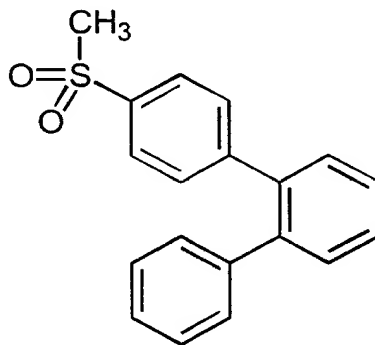
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40)



[1,1':2',1''-terphenyl]-4-sulfonamide,

41)

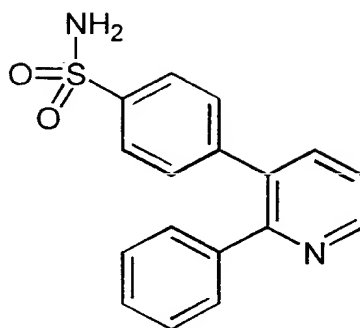


10

4-(methylsulfonyl)-1,1',2],1''-terphenyl,

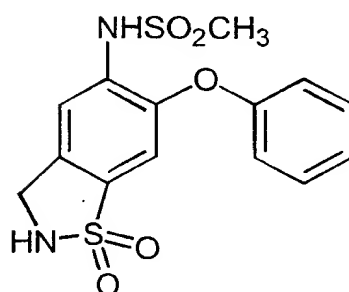
-234-

42)



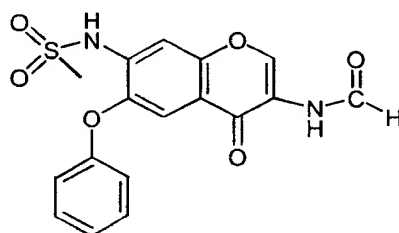
4-(2-phenyl-3-pyridinyl)benzenesulfonamide,

43)



N-(2,3-dihydro-1,1-dioxido-6-phenoxy-1,2-benzisothiazol-5-yl)methanesulfonamide, and

44)

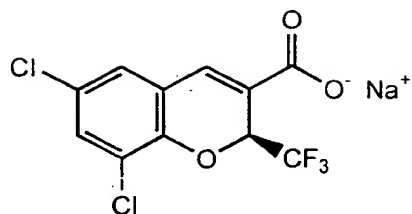


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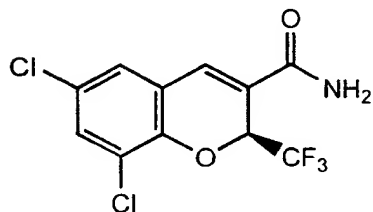
N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl]methanesulfonamide,

-235-

45)

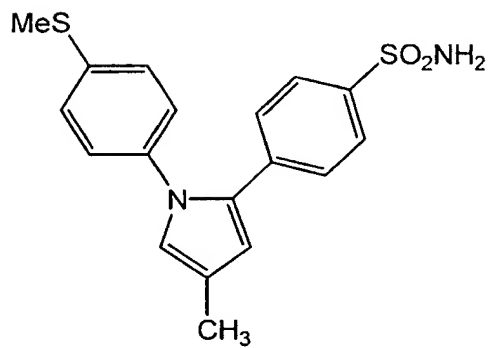


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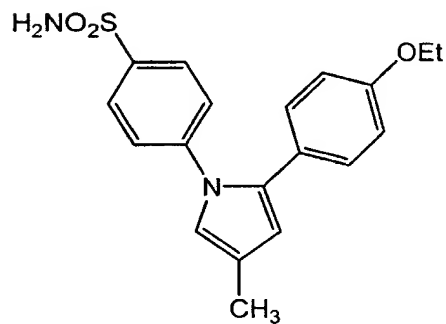
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47)



, and

48)

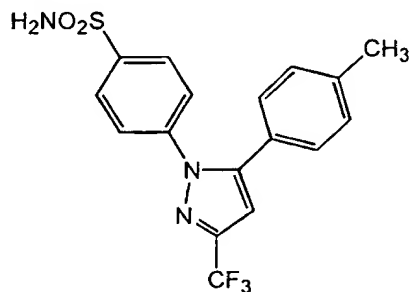


35. The method of Claim 1 wherein the
 10 cyclooxygenase-2 inhibitor is 5-chloro-3-(4-(methylsulfonyl)phenyl)-2-(methyl-5-pyridinyl)pyridine.

-236-

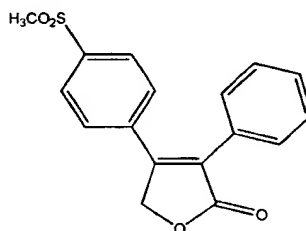
36. The method of Claim 1 wherein the cyclooxygenase-2 inhibitor is 2-(3,5-difluorophenyl)-3-4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one.

37. The method of Claim 1 wherein the
5 cyclooxygenase-2 inhibitor is



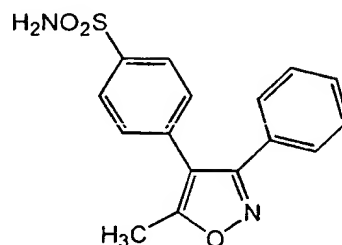
4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-benzenesulfonamide.

38. The method of Claim 1 wherein the
10 cyclooxygenase-2 inhibitor is



rofecoxib, 4-(4-(methylsulfonyl)phenyl)-3-phenyl-2(5H)-furanone.

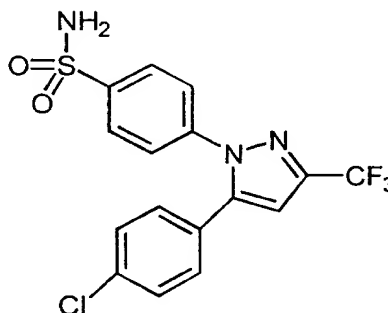
39. The method of Claim 1 wherein the cyclooxygenase-2 inhibitor is



5 4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide.

40. The method of Claim 1 wherein the cyclooxygenase-2 inhibitor is N-[[4-(5-methyl-3-phenylisoxazol-4yl)phenyl]sulfonyl]propanamide.

41. The method of Claim 1 wherein the
10 cyclooxygenase-2 inhibitor is



4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl]benzenesulfonamide.

42. The method of Claim 1 wherein the neoplasia is
15 selected from the group consisting of lung cancer, breast cancer, gastrointestinal cancer, bladder cancer, head and neck cancer and cervical cancer.

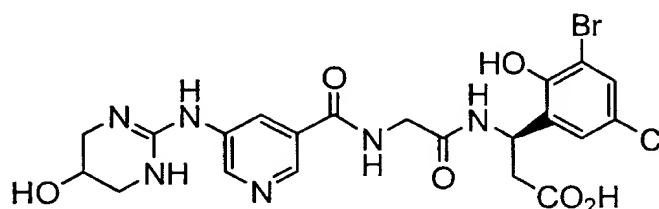
43. The method of Claim 1 wherein the neoplasia is
20 selected from the group consisting of acral lentiginous melanoma, actinic keratoses, adenocarcinoma, adenoid cystic carcinoma, adenomas, adenosarcoma, adenosquamous carcinoma, astrocytic tumors, bartholin gland carcinoma,

basal cell carcinoma, bronchial gland carcinomas,
capillary, carcinoids, carcinoma, carcinosarcoma,
cavernous, cholangiocarcinoma, chondrosarcoma, choroid
plexus papilloma/carcinoma, clear cell carcinoma,
5 cystadenoma, endodermal sinus tumor, endometrial
hyperplasia, endometrial stromal sarcoma, endometrioid
adenocarcinoma, ependymal, epithelioid, Ewing's sarcoma,
fibrolamellar, focal nodular hyperplasia, gastrinoma,
germ cell tumors, glioblastoma, glucagonoma,
10 hemangiblastomas, hemangioendothelioma, hemangiomas,
hepatic adenoma, hepatic adenomatosis, hepatocellular
carcinoma, insulinoma, intraepithelial neoplasia,
interepithelial squamous cell neoplasia, invasive
squamous cell carcinoma, large cell carcinoma,
15 leiomyosarcoma, lentigo maligna melanomas, malignant
melanoma, malignant mesothelial tumors, medulloblastoma,
medulloepithelioma, melanoma, meningeal, mesothelial,
metastatic carcinoma, mucoepidermoid carcinoma,
neuroblastoma, neuroepithelial adenocarcinoma nodular
20 melanoma, oat cell carcinoma, oligodendroglial,
osteosarcoma, pancreatic polypeptide, papillary serous
adenocarcinoma, pineal cell, pituitary tumors,
plasmacytoma, pseudosarcoma, pulmonary blastoma, renal
cell carcinoma, retinoblastoma, rhabdomyosarcoma,
25 sarcoma, serous carcinoma, small cell carcinoma, soft
tissue carcinomas, somatostatin-secreting tumor,
squamous carcinoma, squamous cell carcinoma,
submesothelial, superficial spreading melanoma,
undifferentiated carcinoma, uveal melanoma, verrucous
30 carcinoma, vipoma, well differentiated carcinoma, and
Wilm's tumor.

44. The method of Claim 1 wherein the integrin antagonist is selected from compounds, and their pharmaceutically acceptable salts thereof, of the group

5 consisting of:

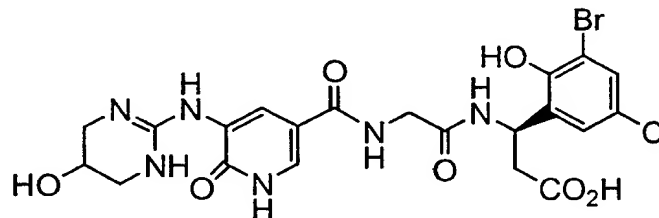
1)



(3R)-N-[[5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]-

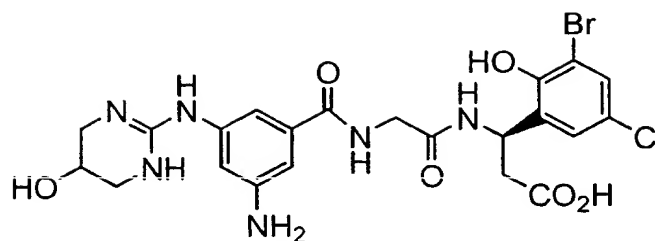
3-pyridinyl]carbonyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine,

2)



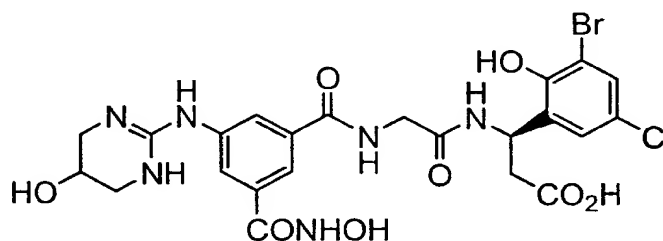
(3R)-N-[[1,6-dihydro-6-oxo-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]-3-pyridinyl]carbonyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine,

3)



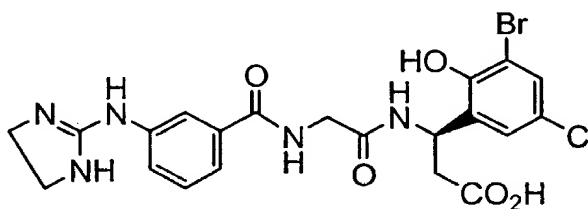
(3R)-N-[3-amino-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-L-alanine,

4)



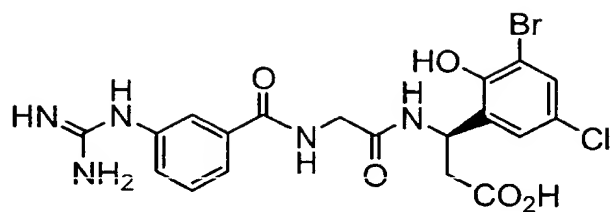
(3R)-N-[3-[(hydroxyamino)carbonyl]-5-[(1,4,5,6-tetrahydro-5-hydroxy)-2-pyrimidinyl]amino]benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-L-alanine,

5)



(3R)-N-[3-[(4,5-dihydro-1H-imidazol-2-yl)amino]benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-L-alanine,

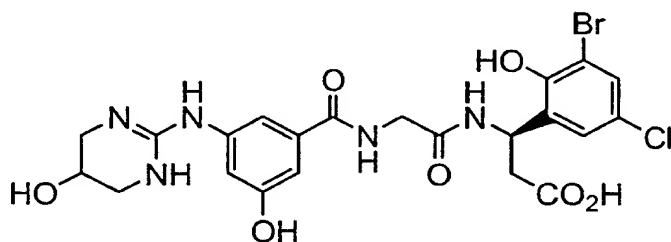
6)



(3R) -N- [3-

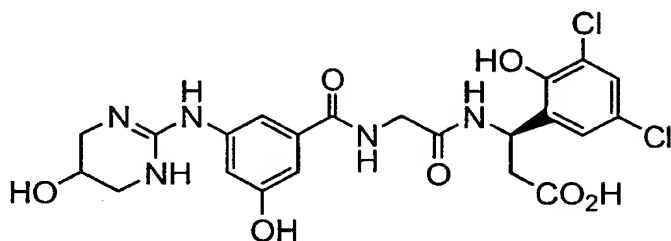
[(aminoiminomethyl) amino] benzoyl] glycyl-3- (3-
bromo-5-chloro-2-hydroxyphenyl) -b-alanine,

7)



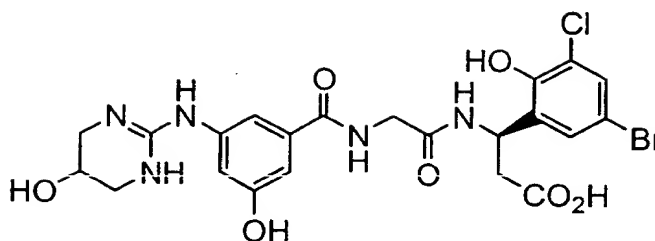
(3R) -N- [3-hydroxy-5- [(1,4,5,6-tetrahydro-5-
hydroxy-2-pyrimidinyl) amino] benzoyl] glycyl-3-
(3-bromo-5-chloro-2-hydroxyphenyl) -b-alanine,

8)



(3R) -N- [3-hydroxy-5- [(1,4,5,6-tetrahydro-5-
hydroxy-2-pyrimidinyl) amino] benzoyl] glycyl-3-
(3,5-dichloro-2-hydroxyphenyl) -b-alanine,

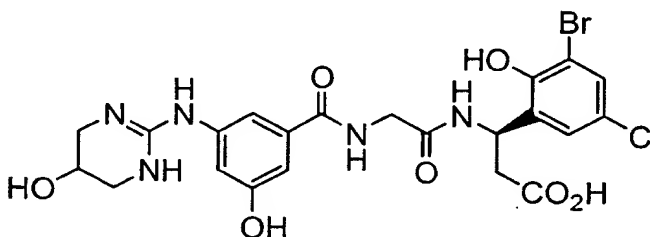
9)



5

(3R) -N - [3-hydroxy-5 - [(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl) amino]benzoyl]glycyl-3-(5-bromo-3-chloro-2-hydroxyphenyl) -b-alanine,

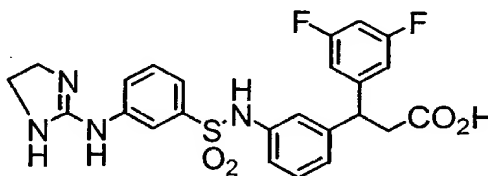
10)



10

(3R) -N - [3-hydroxy-5 - [(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl) amino]benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl) -b-alanine,

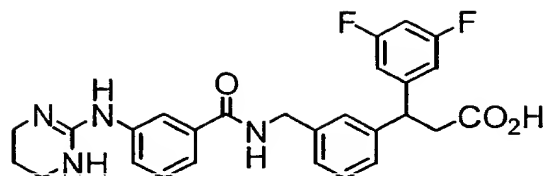
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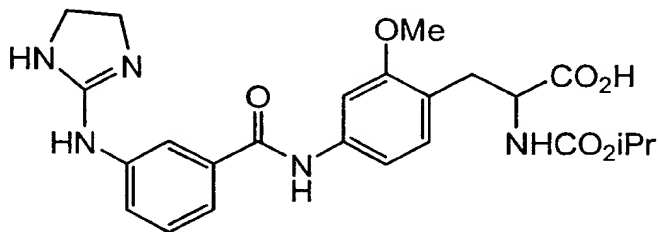
b - [3 - [[[3 - [[4,5-dihydro-1H-imidazol-2-yl) amino]phenyl]sulfonyl] amino]phenyl] -3,5-difluorobenzenepropanoic acid,

12)

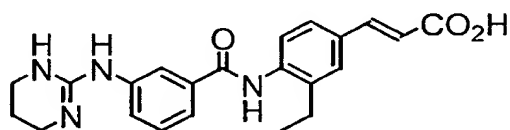


3,5-difluoro-b-[3-[[[3-[(1,4,5,6-tetrahydro-2-pyrimidinyl)amino]benzoyl]amino]methyl]phenyl] benzenepropanoic acid,

13)

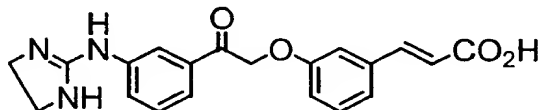


14)



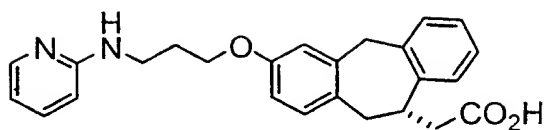
(2E)-3-[3-ethyl-4-[[3-[(1,4,5,6-tetrahydro-2-pyrimidinyl)amino]benzoyl]amino]phenyl]-2-propenoic acid,

15)



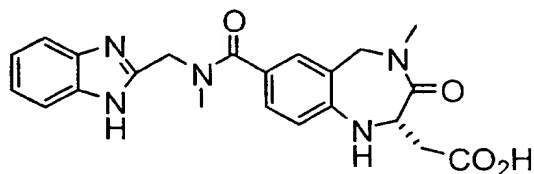
(2E)-3-[3-ethyl-4-[[3-[(1,4,5,6-tetrahydro-2-pyrimidinyl)amino]benzoyl]amino]phenyl]-2-propenoic acid,

16)



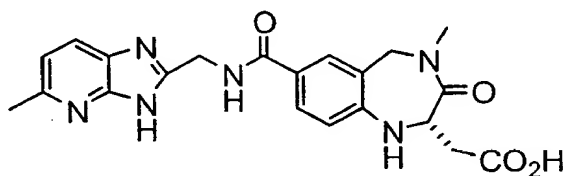
(10S)-10,11-dihydro-3-[3-(2-pyridinylamino)propoxy]-5H-dibenzo[a,d]cycloheptene-10-acetic acid,

17)



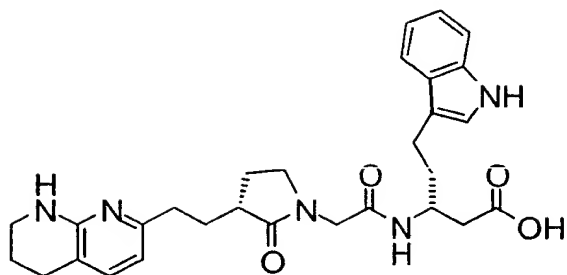
(2S)-7-[[[(1H-benzimidazol-2-ylmethyl)methylamino]carbonyl]-2,3,4,5-tetrahydro-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid,

18)



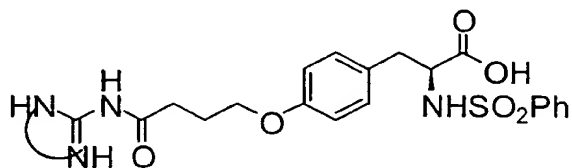
(2S)-2,3,4,5-tetrahydro-4-methyl-7-[[[(5-methyl-1H-imidazo[4,5-b]pyridin-2-yl)methyl]amino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid,

19)

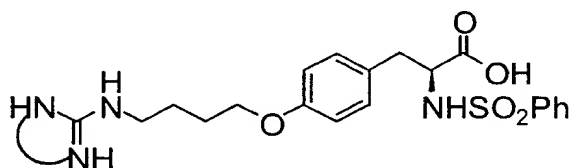


(bR) -b-[[[(3R)-2-oxo-3-[2-(1,5,6,7-tetrahydro-1,8-naphthyridin-2-yl)ethyl]-1-pyrrolidinyl]acetyl]amino]-1H-indole-3-pentanoic acid,

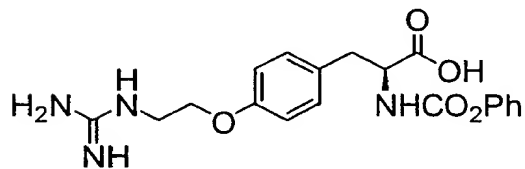
20)



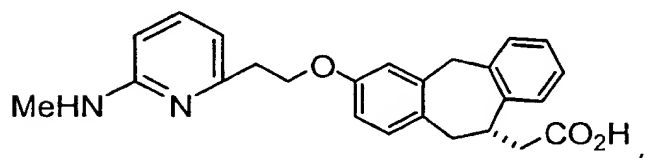
21)



22)



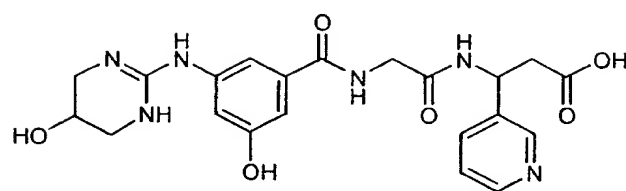
23)



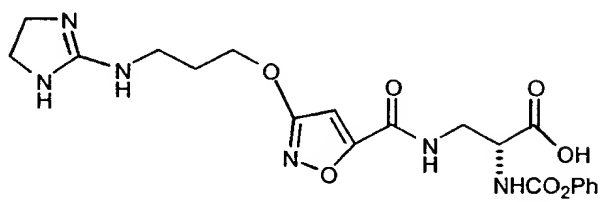
24) Vitaxin antibody(Ixsys),

25) Merck KGaA EMD-121974, cyclo[RGDf-N(Me)V-],

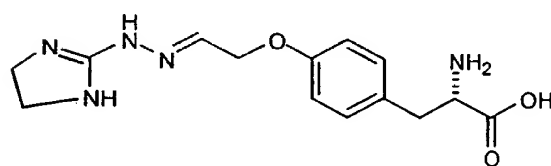
26)

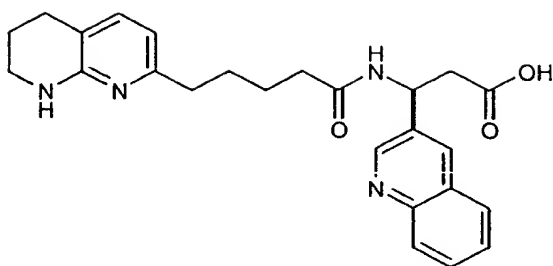


27)

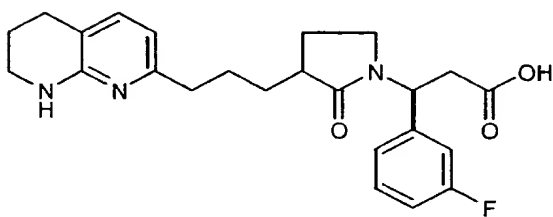


28)

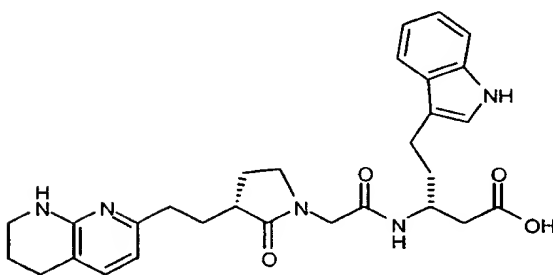




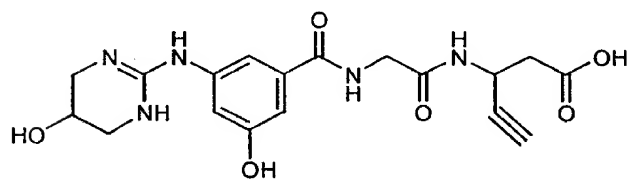
30)



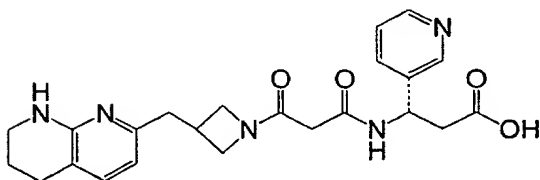
31)



32)

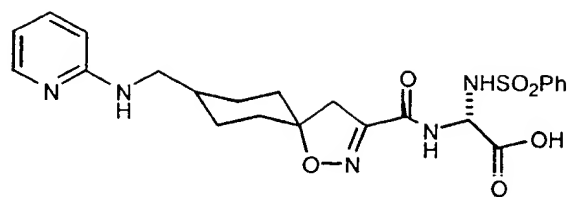


33)



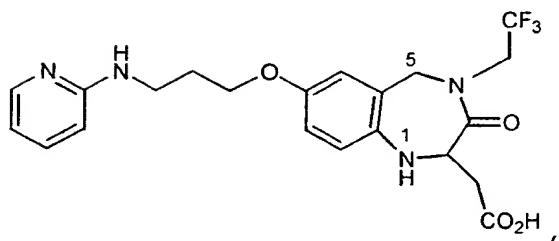
-248-

34)

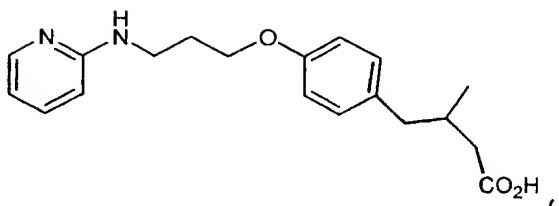


35)

5

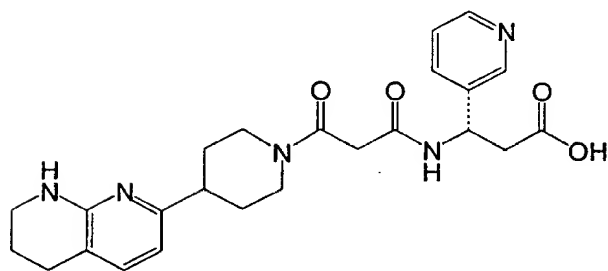


36)

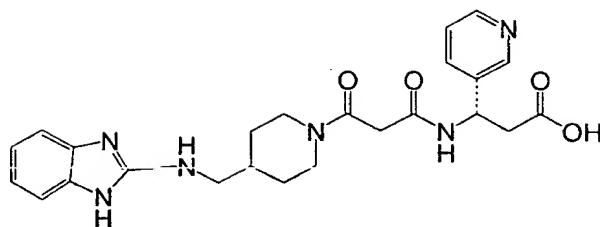


37)

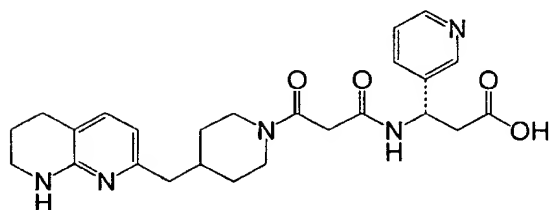
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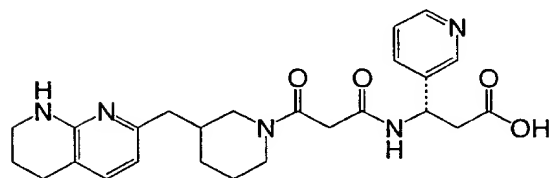
38)



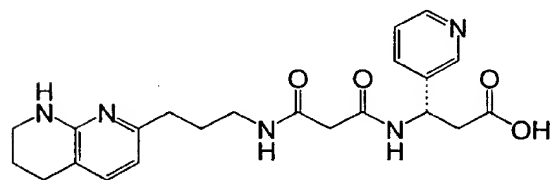
39)



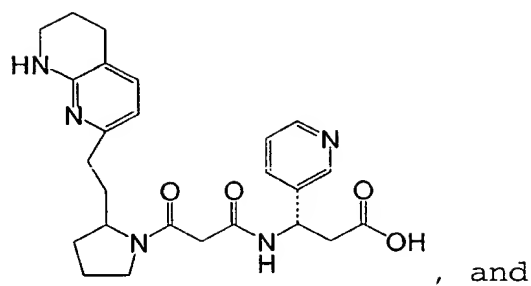
40)



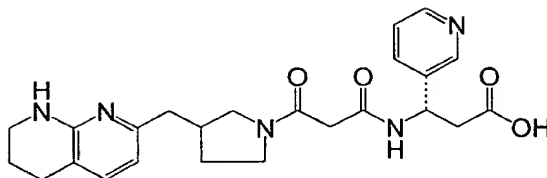
41)



42)

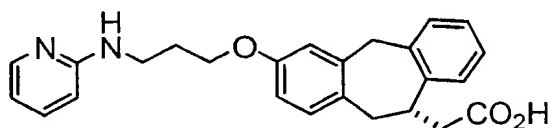


43)



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45. The method of Claim 1 wherein the integrin antagonist is

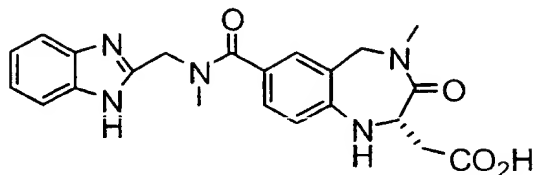


10

(10S)-10,11-dihydro-3-[3-(2-pyridinylamino)propoxy]-5H-dibenzo[a,d]cycloheptene-10-acetic acid.

-251-

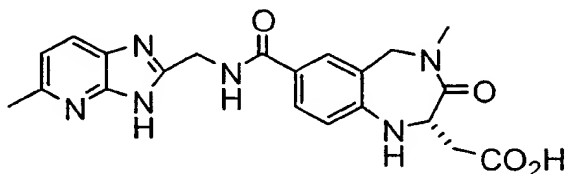
46. The method of Claim 1 wherein the integrin antagonist is



5

(2S)-7-[[[(1H-benzimidazol-2-ylmethyl)methylamino]carbonyl]-2,3,4,5-tetrahydro-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid.

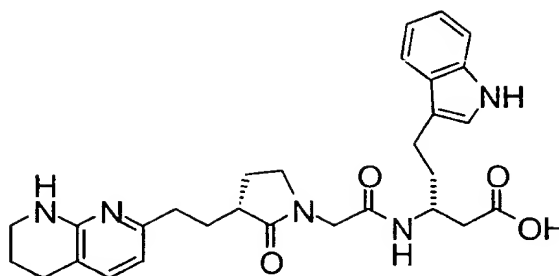
47. The method of Claim 1 wherein the integrin antagonist is



10

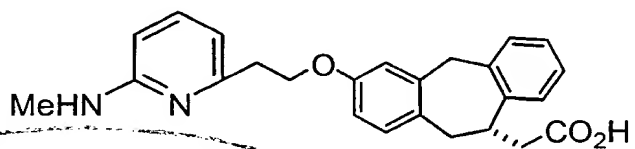
(2S)-2,3,4,5-tetrahydro-4-methyl-7-[[[(5-methyl-1H-imidazo[4,5-b]pyridin-2-yl)methyl]amino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid.

48. The method of Claim 1 wherein the integrin antagonist is



5 (bR)-b-[[[(3R)-2-oxo-3-[2-(1,5,6,7-tetrahydro-1,8-naphthyridin-2-yl)ethyl]-1-pyrrolidinyl]acetyl]amino]-1H-indole-3-pentanoic acid.

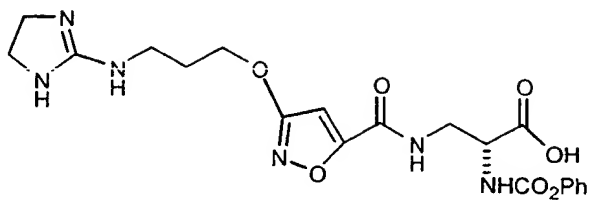
49. The method of Claim 1 wherein the integrin
10 antagonist is



50. The method of Claim 1 wherein the integrin
15 antagonist is Vitaxin antibody(Ixsys).

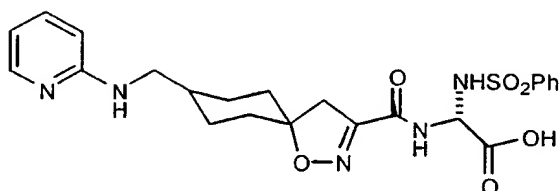
51. The method of Claim 1 wherein the integrin antagonist is Merck KGaA EMD-121974, cyclo[RGDf-N(Me)V-]

52. The method of Claim 1 wherein the integrin antagonist is



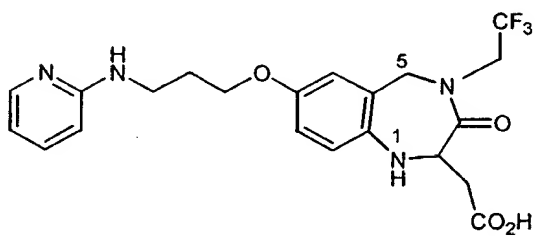
5

53. The method of Claim 1 wherein the integrin antagonist is



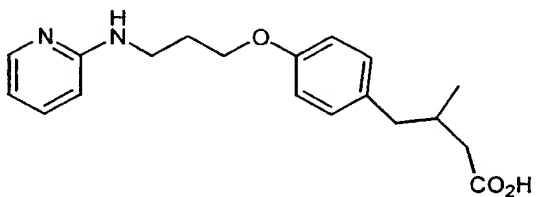
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54. The method of Claim 1 wherein the integrin antagonist is



15

55. The method of Claim 1 wherein the integrin antagonist is



56. A method for treating or preventing a neoplasia disorder in a mammal in need of such treatment or prevention, which method comprises administering to said mammal a therapeutically-effective amount of a
5 combination of radiation, a cyclooxygenase-2 inhibitor, an integrin antagonist, and an antineoplastic agent, wherein said antineoplastic agent is selected from the group consisting of anastrozole, calcium carbonate, capecitabine, carboplatin, cisplatin, Cell Pathways CP-
10 461, docetaxel, doxorubicin, etoposide, fluorouracil (5-FU), fluoxymestrine, gemcitabine, goserelin, irinotecan, ketoconazole, letrozol, leucovorin, levamisole, megestrol, mitoxantrone, paclitaxel, raloxifene, retinoic acid, tamoxifen, thiotepa, topotecan,
15 toremifene, vinorelbine, vinblastine, vincristine, selenium (selenomethionine), ursodeoxycholic acid, sulindac sulfone, exemestane and eflornithine (DFMO).

57. The method of Claim 56 wherein the combination
20 is administered in a sequential manner.

58. The method of Claim 56 wherein the combination is administered in a substantially simultaneous manner.

25 59. The method of Claim 56 wherein the antineoplastic agent is capecitabine.

60. The method of Claim 56 wherein the antineoplastic agent is carboplatin.

61. The method of Claim 56 wherein the antineoplastic agent is cisplatin.

5 62. The method of Claim 56 wherein the antineoplastic agent is Cell Pathways CP-461.

63. The method of Claim 56 wherein the antineoplastic agent is docetaxel.

10

64. The method of Claim 56 wherein the antineoplastic agent is doxorubicin.

15 65. The method of Claim 56 wherein the antineoplastic agent is etoposide.

66. The method of Claim 56 wherein the antineoplastic agent is fluoxymestrine.

20 67. The method of Claim 56 wherein the antineoplastic agent is gemcitabine.

68. The method of Claim 56 wherein the antineoplastic agent is goserelin.

25

69. The method of Claim 56 wherein the antineoplastic agent is irinotecan.

30 70. The method of Claim 56 wherein the antineoplastic agent is ketoconazole.

-256-

72. The method of Claim 56 wherein the antineoplastic agent is letrozol.

73. The method of Claim 56 wherein the
5 antineoplastic agent is leucovorin.

74. The method of Claim 56 wherein the antineoplastic agent is levamisole.

10 75. The method of Claim 56 wherein the antineoplastic agent is megestrol.

76. The method of Claim 56 wherein the antineoplastic agent is mitoxantrone.
15

77. The method of Claim 56 wherein the antineoplastic agent is paclitaxel.

78. The method of Claim 56 wherein the
20 antineoplastic agent is raloxifene.

79. The method of Claim 56 wherein the antineoplastic agent is retinoic acid.

25 80. The method of Claim 56 wherein the antineoplastic agent is tamoxifen.

81. The method of Claim 56 wherein the antineoplastic agent is thiotepa.
30

-257-

82. The method of Claim 56 wherein the antineoplastic agent is topotecan.

83. The method of Claim 56 wherein the
5 antineoplastic agent is toremifene.

84. The method of Claim 56 wherein the antineoplastic agent is vinorelbine.

10 85. The method of Claim 56 wherein the antineoplastic agent is vinblastine.

86. The method of Claim 56 wherein the antineoplastic agent is vincristine.

15 87. The method of Claim 56 wherein the antineoplastic agent is selenium (selenomethionine).

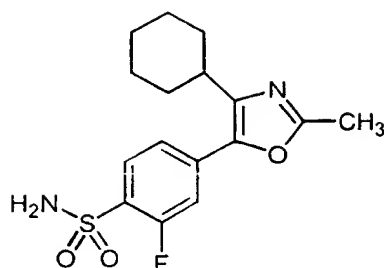
88. The method of Claim 56 wherein the
20 antineoplastic agent is sulindac sulfone.

89. The method of Claim 56 wherein the antineoplastic agent is eflornithine (DFMO).

25 90. The method of Claim 56 wherein the cyclooxygenase-2 inhibitor is selected from compounds, and their pharmaceutically acceptable salts thereof, of the group consisting of:

-258-

1)



JTE-522, 4-(4-cyclohexyl-2-methyloxazol-5-yl)-
2-fluorobenzenesulfonamide,

5

2)

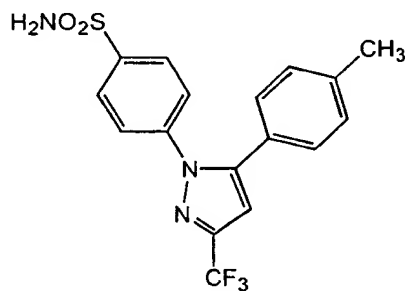
5-chloro-3-(4-(methylsulfonyl)phenyl)-2-
(methyl-5-pyridinyl)pyridine,

3)

2-(3,5-difluorophenyl)-3-4-
(methylsulfonyl)phenyl)-2-cyclopenten-1-one,

10

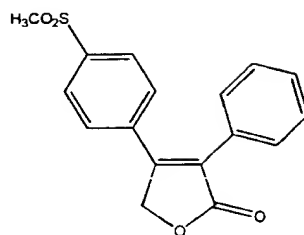
4)



4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-
pyrazol-1-yl]-benzenesulfonamide,

-259-

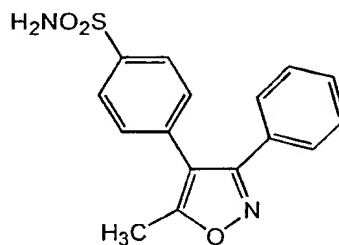
5)



rofecoxib, 4-(4-(methanesulfonyl)phenyl)-3-phenyl-2(5H)-furanone,

5

6)



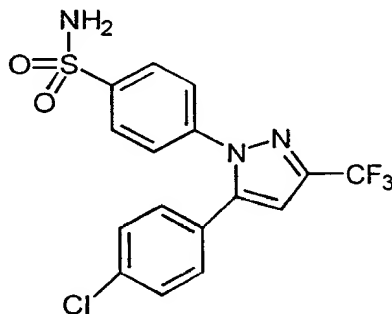
4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide,

7)

N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide,

10

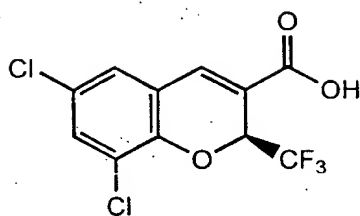
8)



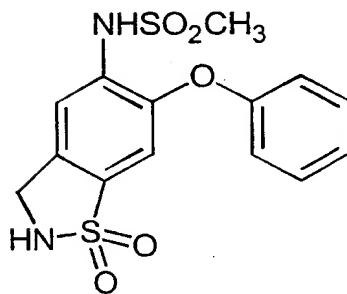
4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl]benzenesulfonamide,

-260-

9)

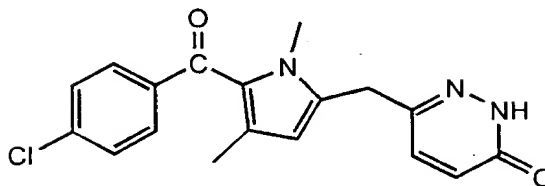


10)



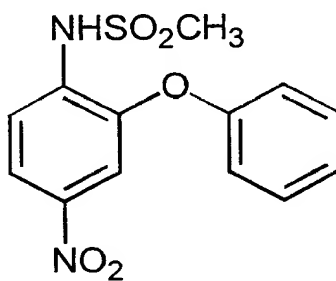
5

11)



6-[[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone,

12)

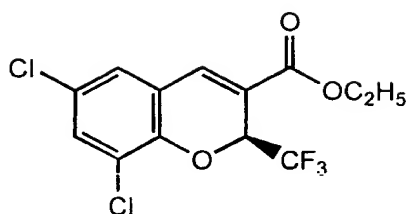


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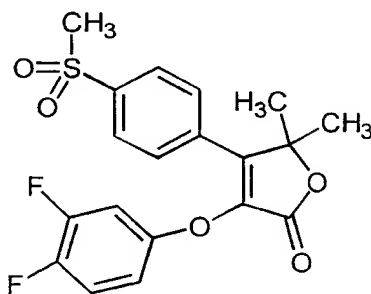
N-(4-nitro-2-phenoxyphenyl)methanesulfonamide,

-261-

13)



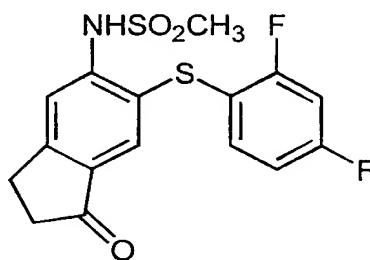
14)



5

3-(3,4-difluorophenoxy)-5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-2(5H)-furanone,

15)

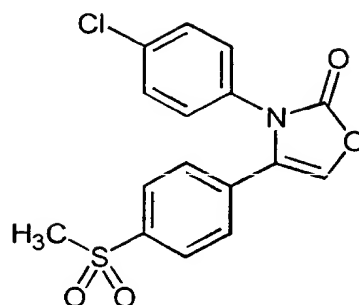


10

N-[6-[(2,4-difluorophenyl)thio]-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide,

-262-

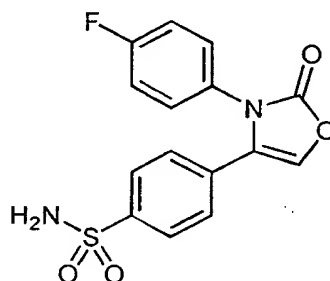
16)



3-(4-chlorophenyl)-4-[4-(methylsulfonyl)phenyl]-2(3H)-oxazolone,

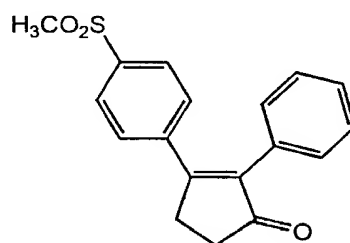
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17)



4-[3-(4-fluorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide,

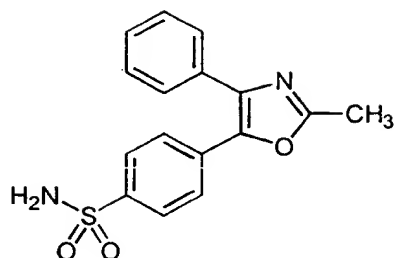
18)



10

3-[4-(methylsulfonyl)phenyl]-2-phenyl-2-cyclopenten-1-one,

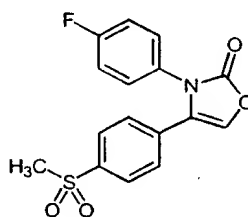
19)



4-(2-methyl-4-phenyl-5-oxazolyl)benzenesulfonamide,

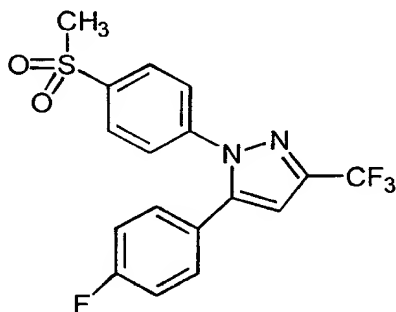
5

20)



3-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2(3H)-oxazolone,

21)

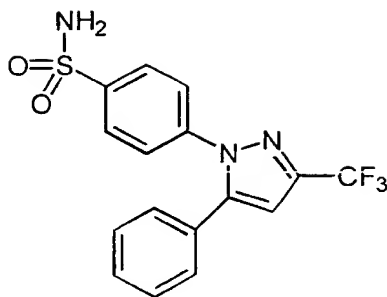


10

5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole,

-264-

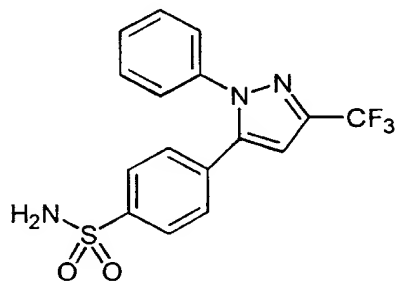
22)



4-[5-phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,

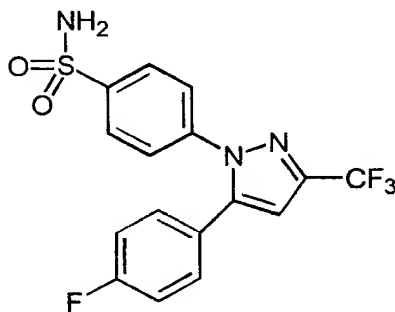
5

23)



4-[1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide,

24)

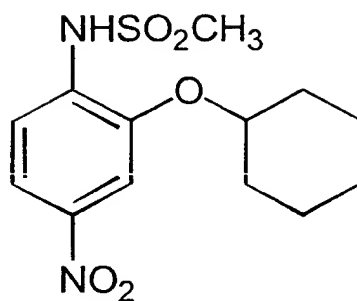


10

4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,

-265-

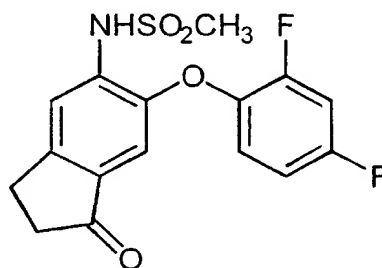
25)



N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide,

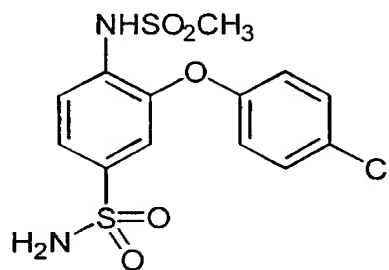
5

26)



N-[6-(2,4-difluorophenoxy)-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide,

27)

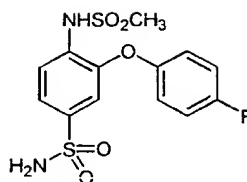


10

3-(4-chlorophenoxy)-4-[(methanesulfonyl)amino]benzenesulfonamide,

-266-

28)

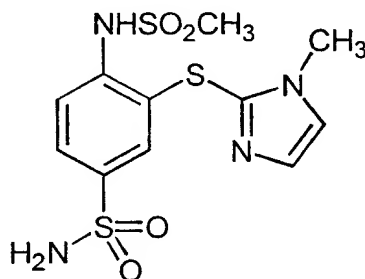


3-(4-fluorophenoxy)-4-

[(methylsulfonyl)amino]benzenesulfonamide,

5

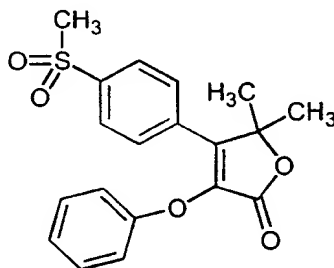
29)



3-[(1-methyl-1H-imidazol-2-yl)thio]-4

[(methylsulfonyl)amino]benzenesulfonamide,

30)

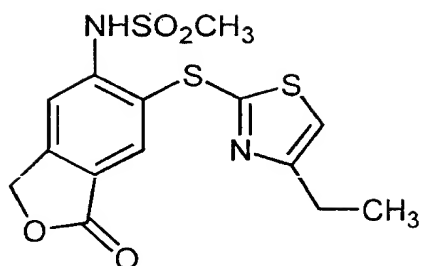


10

5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-3-phenoxy-2(5H)-furanone,

-267-

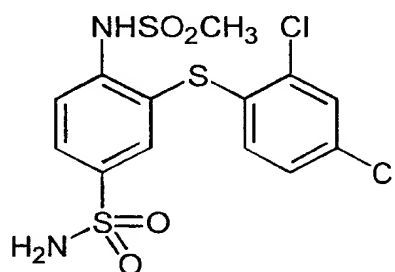
31)



N-[6-[(4-ethyl-2-thiazolyl)thio]-1,3-dihydro-1-oxo-5-isobenzofuranyl]methanesulfonamide,

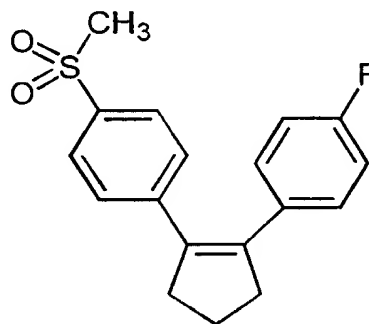
5

32)



3-[(2,4-dichlorophenyl)thio]-4-[(methanesulfonyl)amino]benzenesulfonamide,

33)

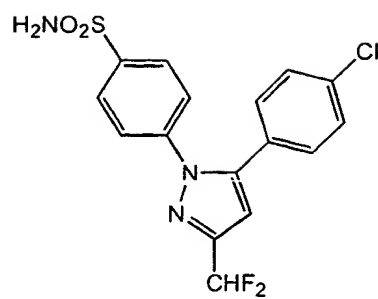


10

1-fluoro-4-[2-[4-(methanesulfonyl)phenyl]cyclopenten-1-yl]benzene,

-268-

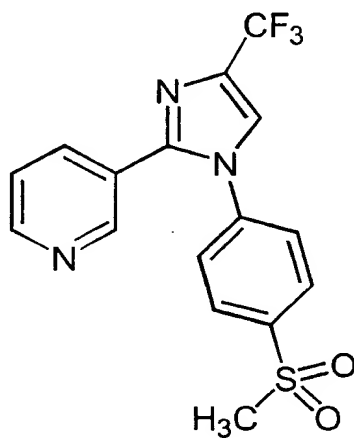
34)



4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,

5

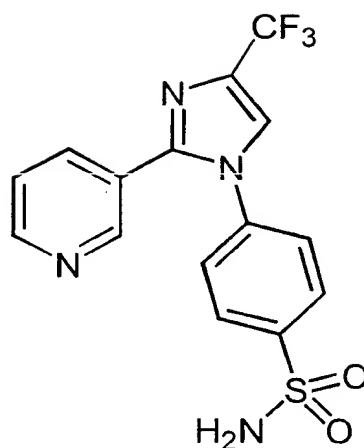
35)



3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine,

-269-

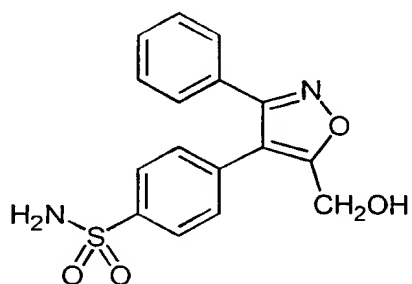
36)



4-[2-(3-pyridinyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide,

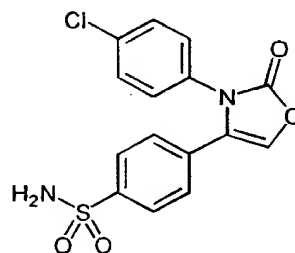
5

37)



4-[5-(hydroxymethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide,

38)

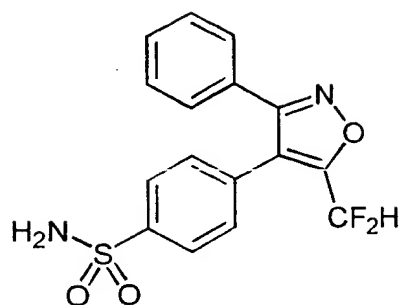


10

4-[3-(4-chlorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide,

-270-

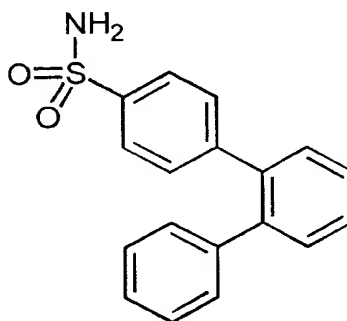
39)



4-[5-(difluoromethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide,

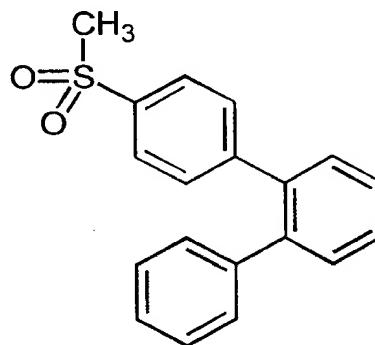
5

40)



[1,1':2',1''-terphenyl]-4-sulfonamide,

41)

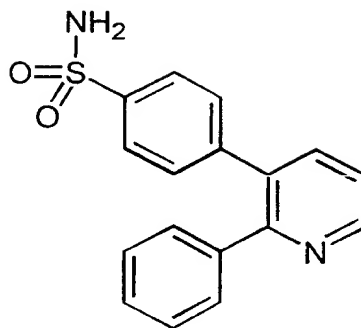


10

4-(methylsulfonyl)-1,1',2],1''-terphenyl,

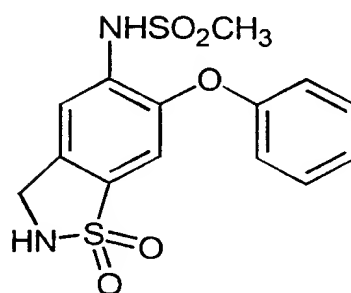
-271-

42)



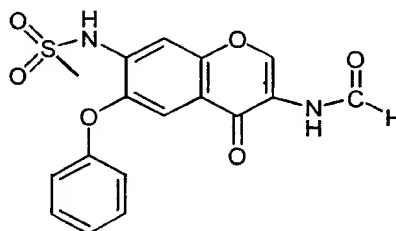
4-(2-phenyl-3-pyridinyl)benzenesulfonamide,

43)



N-(2,3-dihydro-1,1-dioxido-6-phenoxy-1,2-benzisothiazol-5-yl)methanesulfonamide, and

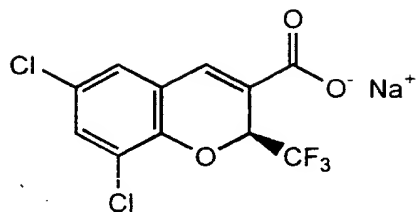
44)



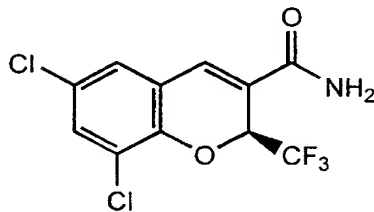
N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl]methanesulfonamide,

-272-

45)

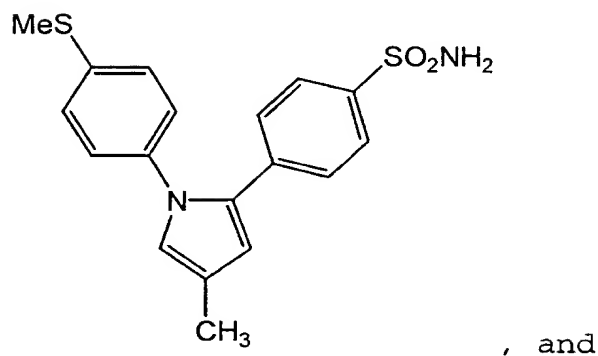


46)

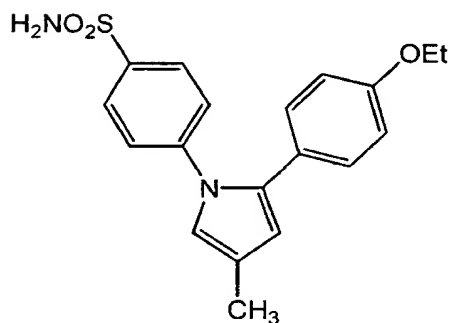


5

47)



48)

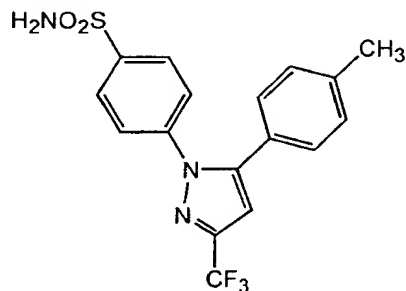


91. The method of Claim 56 wherein the
10 cyclooxygenase-2 inhibitor is 5-chloro-3-(4-(methylsulfonyl)phenyl)-2-(methyl-5-pyridinyl)pyridine.

-273-

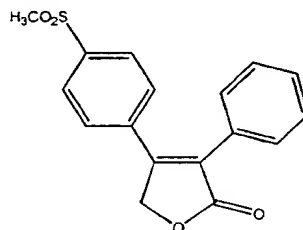
92. The method of Claim 56 wherein the cyclooxygenase-2 inhibitor is 2-(3,5-difluorophenyl)-3-4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one.

93. The method of Claim 56 wherein the
5 cyclooxygenase-2 inhibitor is



4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-benzenesulfonamide.

94. The method of Claim 56 wherein the
10 cyclooxygenase-2 inhibitor is



rofecoxib, 4-(4-(methylsulfonyl)phenyl)-3-phenyl-2(5H)-furanone.

gland carcinoma, basal cell carcinoma, bronchial gland carcinomas, capillary, carcinoids, carcinoma, carcinosarcoma, cavernous, cholangiocarcinoma, chondrosarcoma, choroid plexus papilloma/carcinoma, clear

5 cell carcinoma, cystadenoma, endodermal sinus tumor, endometrial hyperplasia, endometrial stromal sarcoma, endometrioid adenocarcinoma, ependymal, epitheloid, Ewing's sarcoma, fibrolamellar, focal nodular hyperplasia, gastrinoma, germ cell tumors, glioblastoma,

10 glucagonoma, hemangioblastomas, hemangioendothelioma, hemangiomas, hepatic adenoma, hepatic adenomatosis, hepatocellular carcinoma, insulinoma, intraepithelial neoplasia, interepithelial squamous cell neoplasia, invasive squamous cell carcinoma, large cell carcinoma,

15 leiomyosarcoma, lentigo maligna melanomas, malignant melanoma, malignant mesothelial tumors, medulloblastoma, medulloepithelioma, melanoma, meningeal, mesothelial, metastatic carcinoma, mucoepidermoid carcinoma, neuroblastoma, neuroepithelial adenocarcinoma nodular

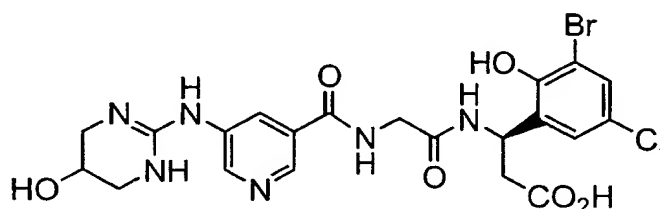
20 melanoma, oat cell carcinoma, oligodendroglial, osteosarcoma, pancreatic polypeptide, papillary serous adenocarcinoma, pineal cell, pituitary tumors, plasmacytoma, pseudosarcoma, pulmonary blastoma, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma,

25 sarcoma, serous carcinoma, small cell carcinoma, soft tissue carcinomas, somatostatin-secreting tumor, squamous carcinoma, squamous cell carcinoma, submesothelial, superficial spreading melanoma, undifferentiated carcinoma, uveal melanoma, verrucous

30 carcinoma, vipoma, well differentiated carcinoma, and Wilm's tumor.

100. The method of Claim 56 wherein the integrin antagonist is selected from compounds, and their pharmaceutically acceptable salts thereof, of the group consisting of:

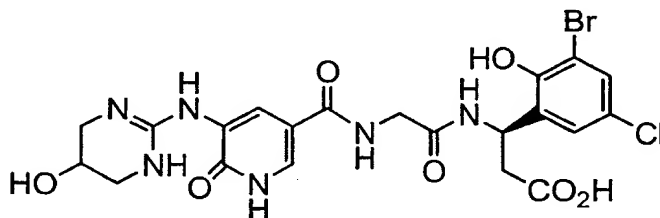
1)



(3R)-N-[[5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]-

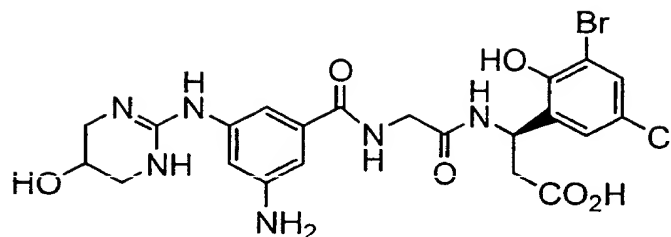
3-pyridinyl]carbonyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-L-alanine,

2)



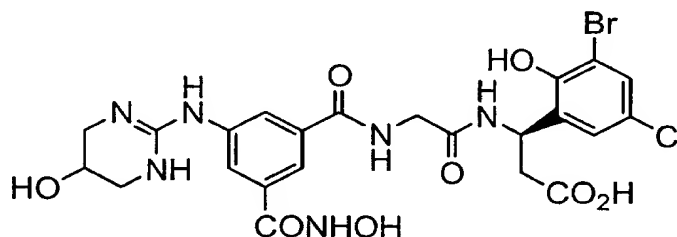
(3R)-N-[[1,6-dihydro-6-oxo-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]-3-pyridinyl]carbonyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-L-alanine,

3)



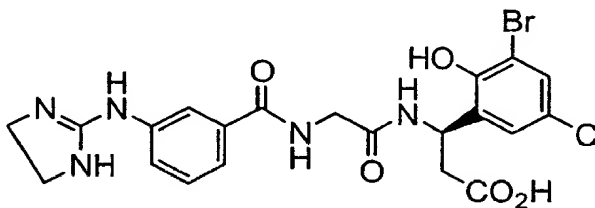
(3R)-N-[3-amino-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine,

4)



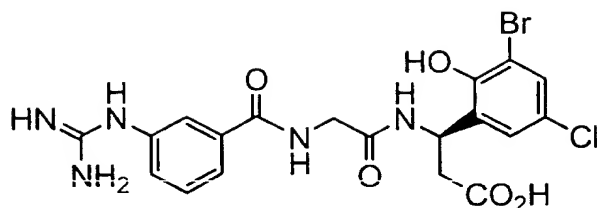
(3R)-N-[3-[(hydroxyamino)carbonyl]-5-[(1,4,5,6-tetrahydro-5-hydroxy)-2-pyrimidinyl]amino]benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine,

5)



(3R)-N-[3-[(4,5-dihydro-1H-imidazol-2-yl)amino]benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine,

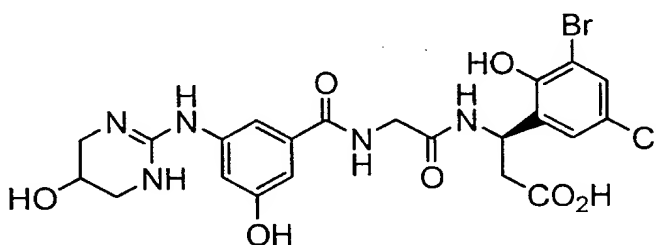
6)



(3R)-N-[3-

[(aminouinomethyl)amino]benzoyl]glycyl-3-(3-
bromo-5-chloro-2-hydroxyphenyl)-L-alanine,

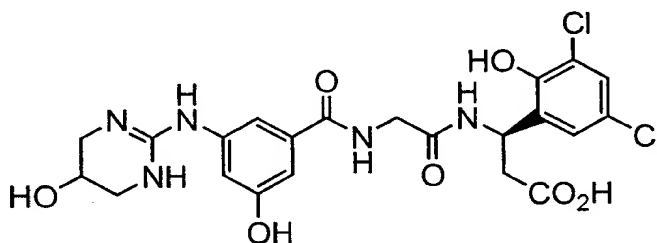
7)



(3R)-N-[3-hydroxy-5-[(1,4,5,6-tetrahydro-5-

hydroxy-2-pyrimidinyl)amino]benzoyl]glycyl-3-
(3-bromo-5-chloro-2-hydroxyphenyl)-L-alanine,

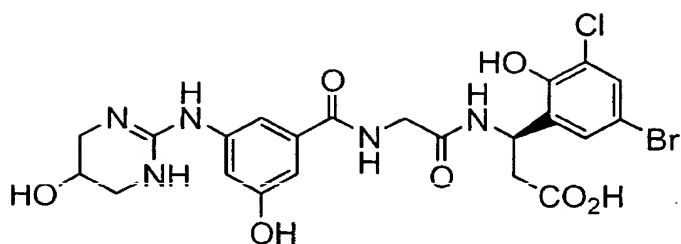
8)



(3R)-N-[3-hydroxy-5-[(1,4,5,6-tetrahydro-5-

hydroxy-2-pyrimidinyl)amino]benzoyl]glycyl-3-
(3,5-dichloro-2-hydroxyphenyl)-L-alanine,

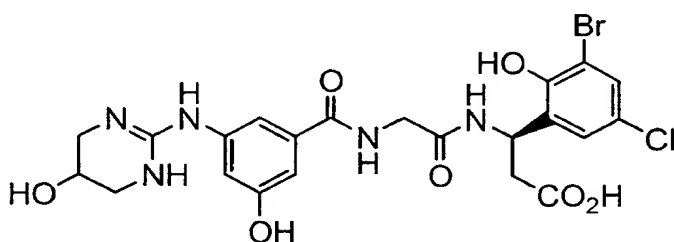
9)



(3R)-N-[3-hydroxy-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]benzoyl]glycyl-3-(5-bromo-3-chloro-2-hydroxyphenyl)-D-alanine,

5

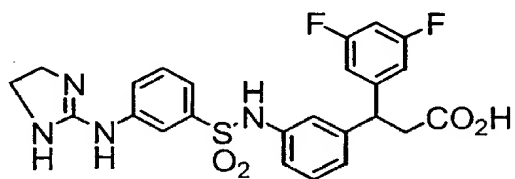
10)



(3R)-N-[3-hydroxy-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-D-alanine,

10

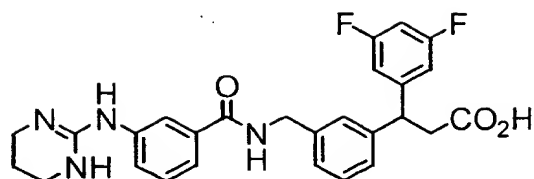
11)



b-[3-[[[3-[[4,5-dihydro-1H-imidazol-2-yl)amino]phenyl]sulfonyl]amino]phenyl]-3,5-difluorobenzenepropanoic acid,

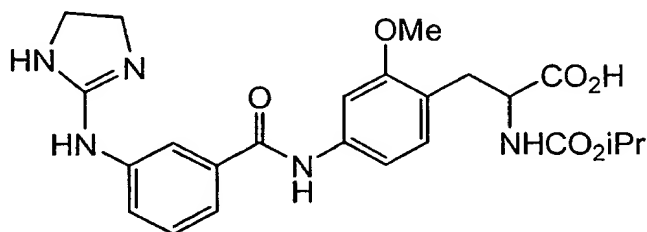
15

12)

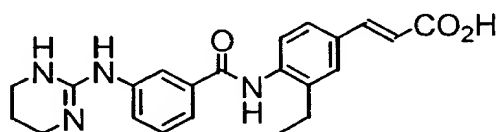


3,5-difluoro-b-[3-[[[3-[(1,4,5,6-tetrahydro-2-pyrimidinyl)amino]benzoyl]amino]methyl]phenyl] benzenepropanoic acid,

13)

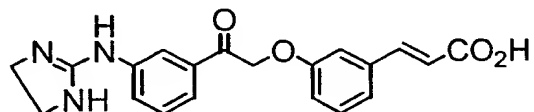


14)



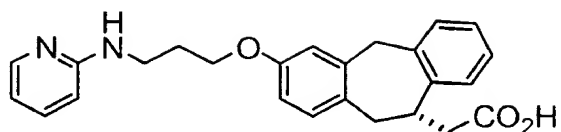
(2E)-3-[3-ethyl-4-[[3-[(1,4,5,6-tetrahydro-2-pyrimidinyl)amino]benzoyl]amino]phenyl]-2-propenoic acid,

15)



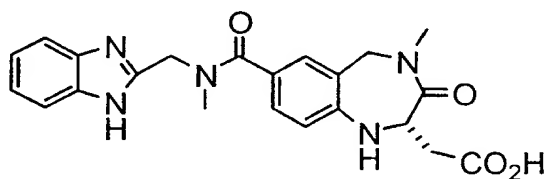
(2E)-3-[3-[2-[3-[(4,5-dihydro-1H-imidazol-2-yl)amino]phenyl]-2-oxoethoxy]phenyl]-2-propenoic acid,

16)



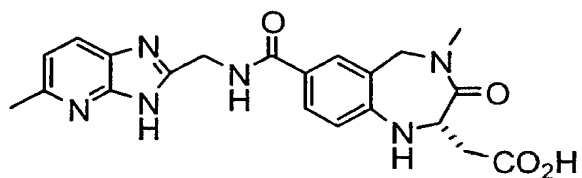
(10S)-10,11-dihydro-3-[3-(2-pyridinylamino)propoxy]-5H-dibenzo[a,d]cycloheptene-10-acetic acid,

17)



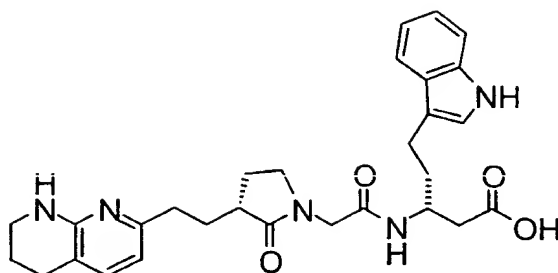
(2S)-7-[[[(1H-benzimidazol-2-ylmethyl)methylamino]carbonyl]-2,3,4,5-tetrahydro-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid,

18)



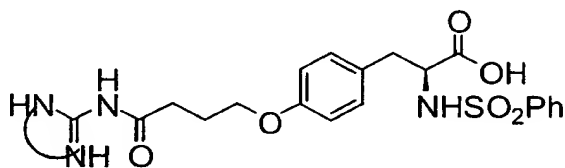
(2S)-2,3,4,5-tetrahydro-4-methyl-7-[[[(5-methyl-1H-imidazo[4,5-b]pyridin-2-yl)methyl]amino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid,

19)



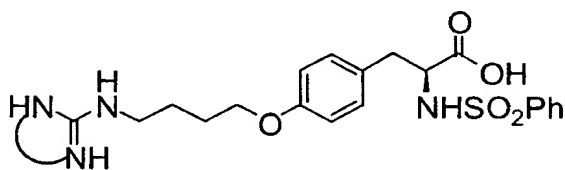
(bR)-b-[[[(3R)-2-oxo-3-[2-(1,5,6,7-tetrahydro-1,8-naphthyridin-2-yl)ethyl]-1-pyrrolidinyl]acetyl]amino]-1H-indole-3-pentanoic acid,

20)

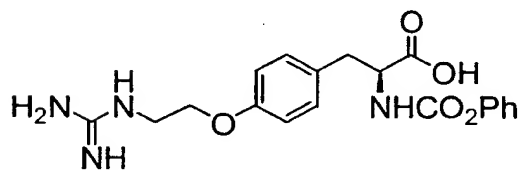


10

21)

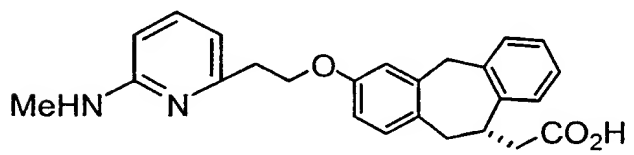


22)



15

23)

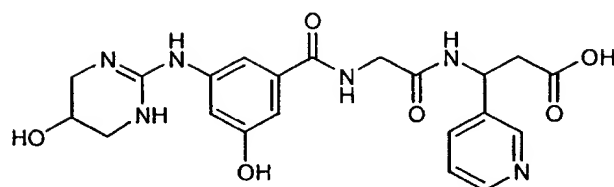


24) Vitaxin antibody(Ixsys),

25) Merck KGaA EMD-121974, cyclo[RGDf-N(Me)V-],

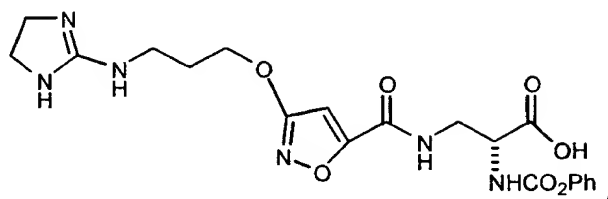
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26)

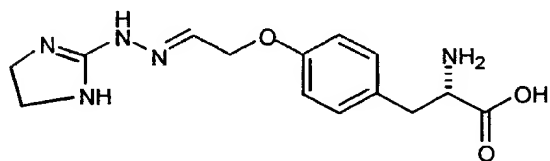


10

27)



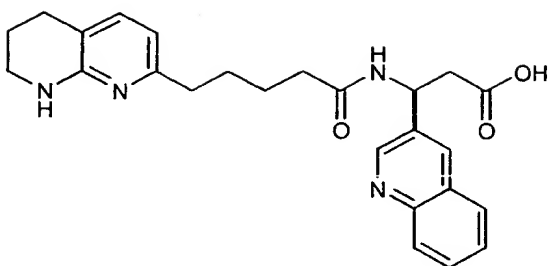
28)



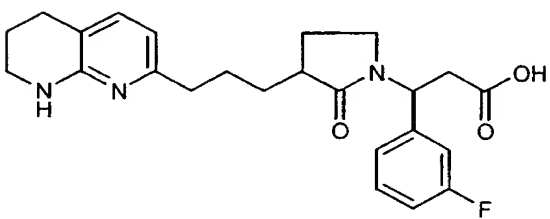
15

-284-

29)

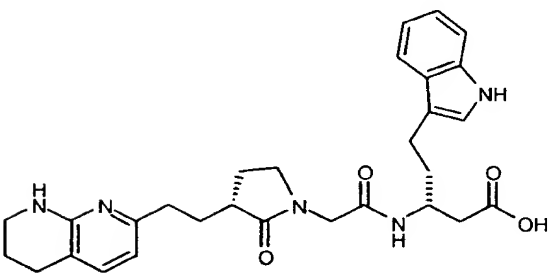


30)

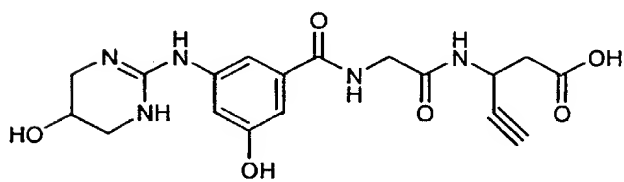


5

31)

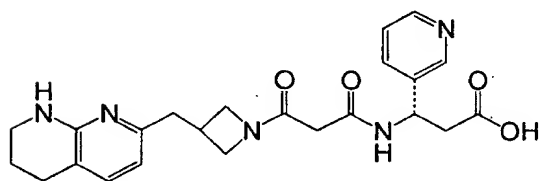


32)



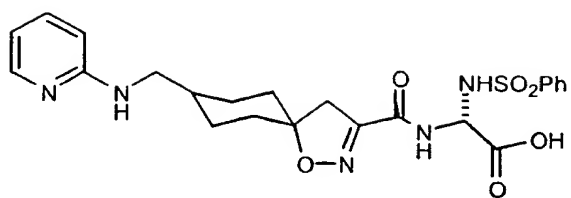
10

33)



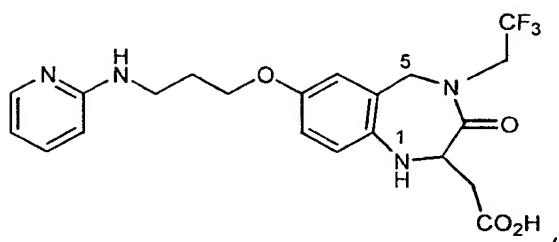
-285-

34)

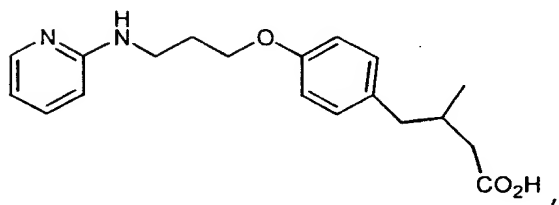


35)

5

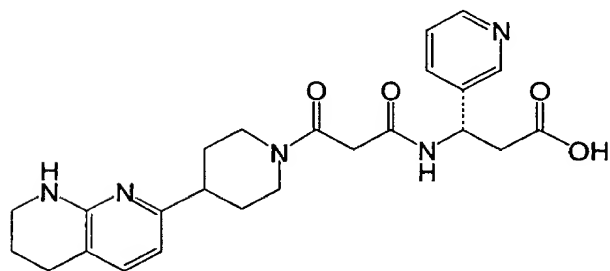


36)

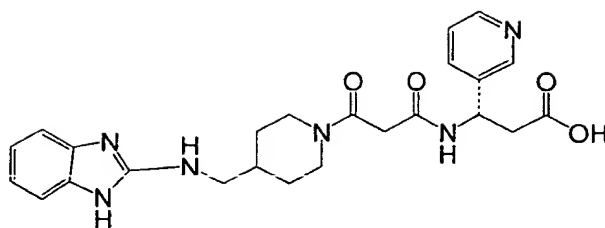


10

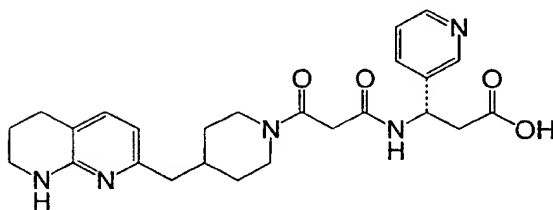
37)



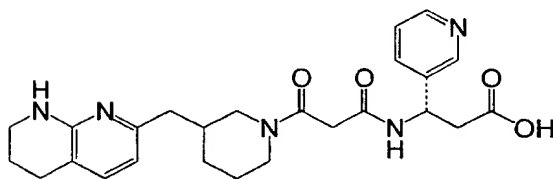
38)



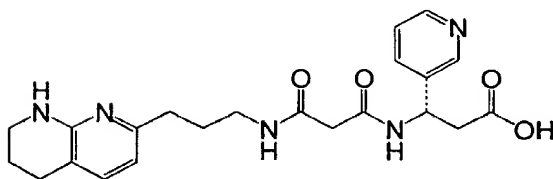
39)



40)

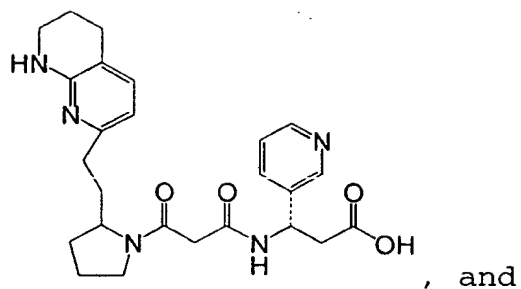


41)

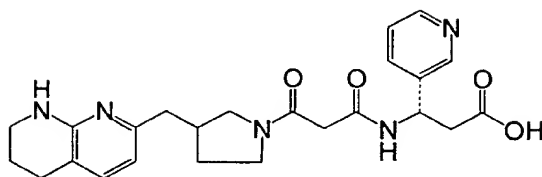


-287-

42)

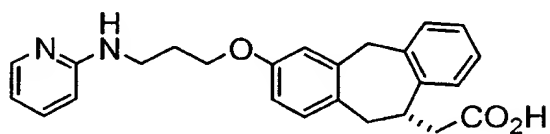


43)



5

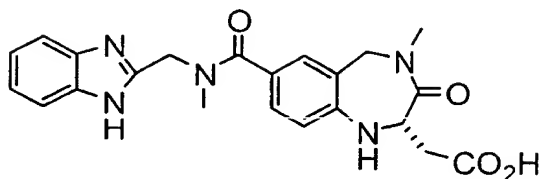
101. The method of Claim 56 wherein the integrin antagonist is



10

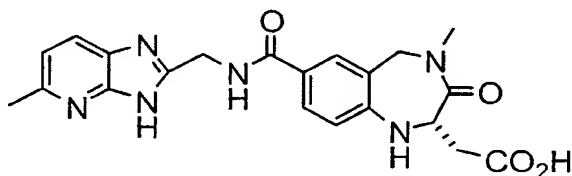
(10S)-10,11-dihydro-3-[3-(2-pyridinylamino)propoxy]-5H-dibenzo[a,d]cycloheptene-10-acetic acid.

102. The method of Claim 56 wherein the integrin antagonist is



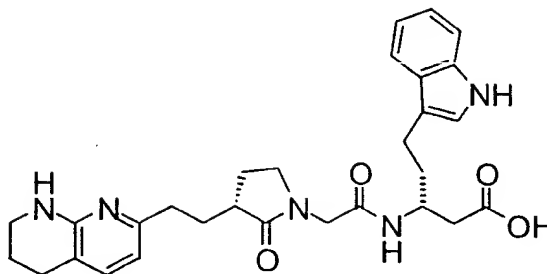
(2S)-7-[[[(1H-benzimidazol-2-ylmethyl)methylamino]carbonyl]-2,3,4,5-tetrahydro-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid.

103. The method of Claim 56 wherein the integrin antagonist is



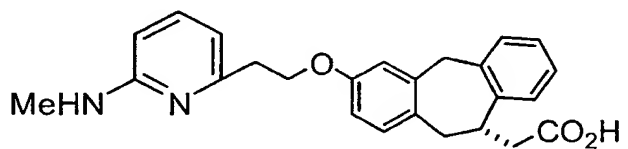
(2S)-2,3,4,5-tetrahydro-4-methyl-7-[[[(5-methyl-1H-imidazo[4,5-b]pyridin-2-yl)methyl]methylamino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid.

104. The method of Claim 56 wherein the integrin antagonist is



5 (bR)-b-[[[(3R)-2-oxo-3-[2-(1,5,6,7-tetrahydro-1,8-naphthyridin-2-yl)ethyl]-1-pyrrolidinyl]acetyl]amino]-1H-indole-3-pentanoic acid.

10 105. The method of Claim 56 wherein the integrin antagonist is

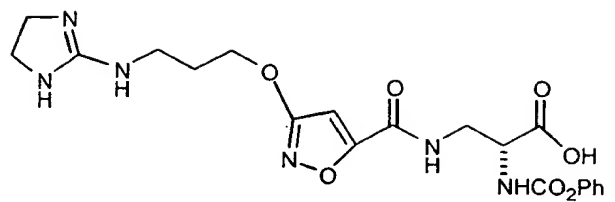


15 106. The method of Claim 56 wherein the integrin antagonist is Vitaxin antibody(Ixsys).

107. The method of Claim 56 wherein the integrin antagonist is Merck KGaA EMD-121974, cyclo[RGDf-N(Me)V-]

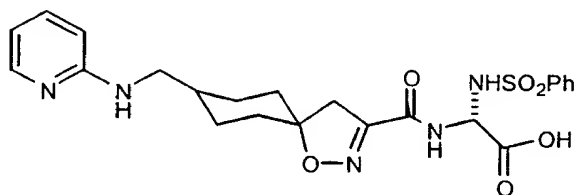
20 108. The method of Claim 56 wherein the integrin antagonist is

-290-



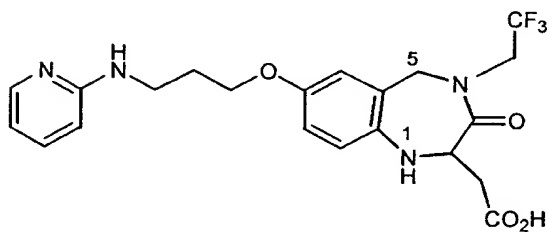
109. The method of Claim 56 wherein the integrin antagonist is

5

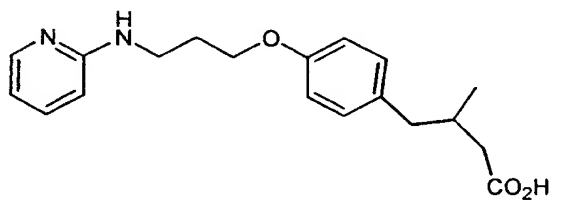


110. The method of Claim 56 wherein the integrin antagonist is

10



111. The method of Claim 56 wherein the integrin antagonist is

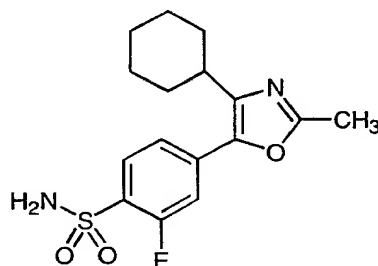


15

112. A combination comprising a cyclooxygenase-2 inhibitor, an integrin antagonist, and an antineoplastic agent, wherein said antineoplastic agent is selected
5 from the group consisting of anastrozole, calcium carbonate, capecitabine, carboplatin, cisplatin, Cell Pathways CP-461, docetaxel, doxorubicin, etoposide, fluorouracil (5-FU), fluoxymestrine, gemcitabine, goserelin, irinotecan, ketoconazole, letrozol,
10 leucovorin, levamisole, megestrol, mitoxantrone, paclitaxel, raloxifene, retinoic acid, tamoxifen, thiotepa, topotecan, toremifene, vinorelbine, vinblastine, vincristine, selenium (selenomethionine), ursodeoxycholic acid, sulindac sulfone, exemestane and
15 eflornithine (DFMO).

113. The combination of Claim 112 wherein the cyclooxygenase-2 inhibitor is selected from compounds, and their pharmaceutically acceptable salts thereof, of
20 the group consisting of:

1)



25 JTE-522, 4-(4-cyclohexyl-2-methyloxazol-5-yl)-
2-fluorobenzenesulfonamide,

2)

-292-

5-chloro-3-(4-(methylsulfonyl)phenyl)-2-(methyl-5-pyridinyl)pyridine,

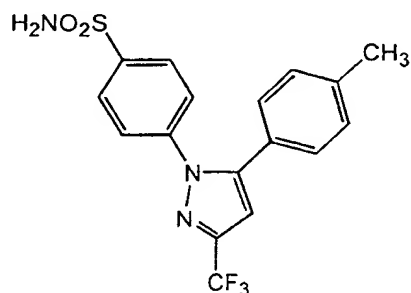
3)

2-(3,5-difluorophenyl)-3-4-

5

(methylsulfonyl)phenyl)-2-cyclopenten-1-one,

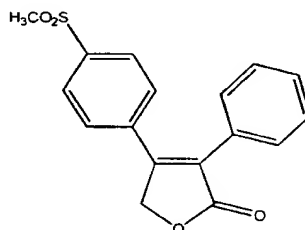
4)



4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-benzenesulfonamide,

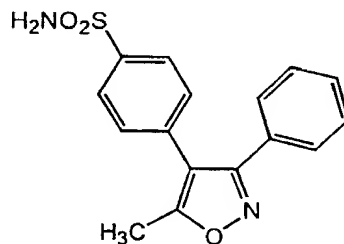
10

5)



rofecoxib, 4-(4-(methylsulfonyl)phenyl)-3-phenyl-2(5H)-furanone,

6)

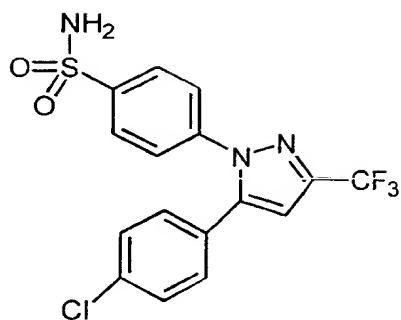


15

4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide,

7) N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide,

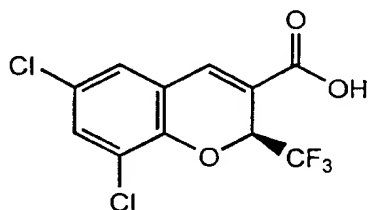
8)



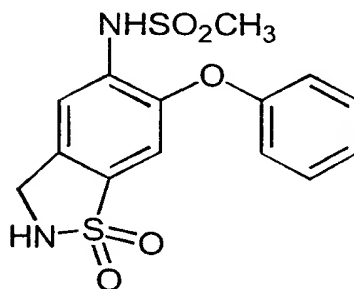
4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl]benzenesulfonamide,

5

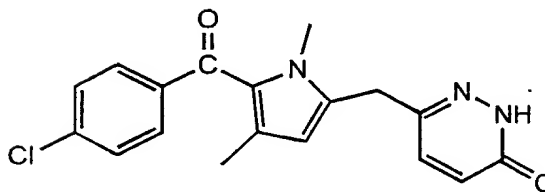
9)



10)



11)

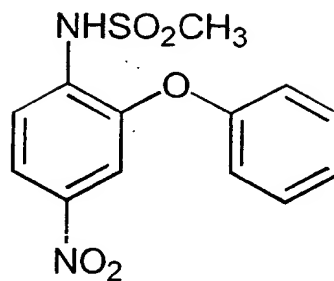


10

6-[[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone,

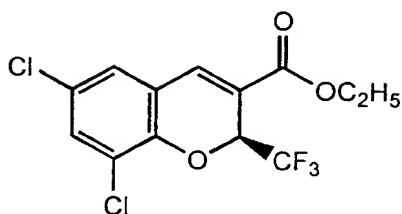
12)

-294-



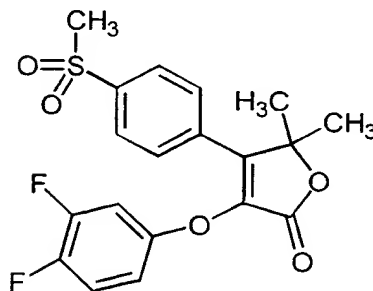
N-(4-nitro-2-phenoxyphenyl)methanesulfonamide,

13)



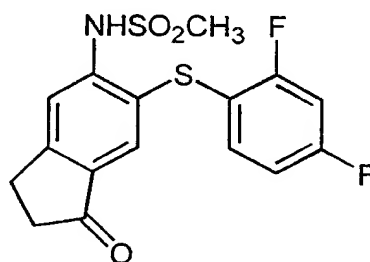
5

14)



3-(3,4-difluorophenoxy)-5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-2(5H)-furanone,

15)

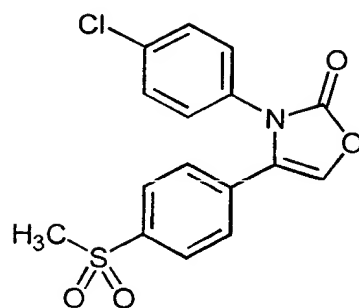


10

N-[6-[(2,4-difluorophenyl)thio]-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide,

-295-

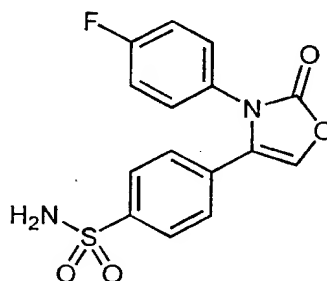
16)



3-(4-chlorophenyl)-4-[4-(methylsulfonyl)phenyl]-2(3H)-oxazolone,

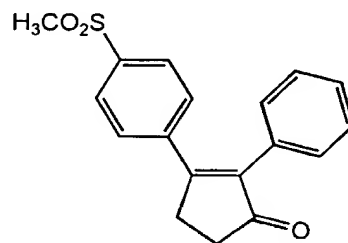
5

17)



4-[3-(4-fluorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide,

18)

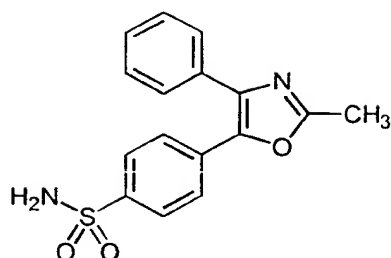


10

3-[4-(methylsulfonyl)phenyl]-2-phenyl-2-cyclopenten-1-one,

-296-

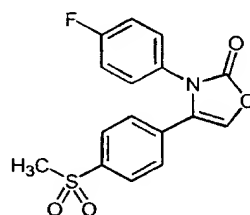
19)



4-(2-methyl-4-phenyl-5-oxazolyl)benzenesulfonamide,

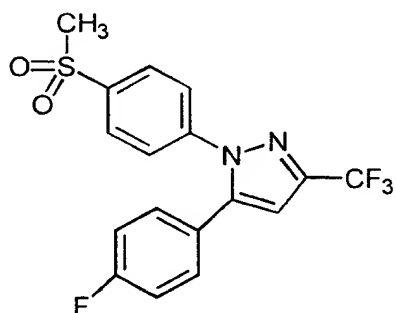
5

20)



3-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2(3H)-oxazolone,

21)

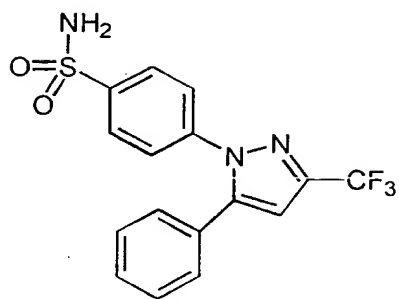


10

5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole,

-297-

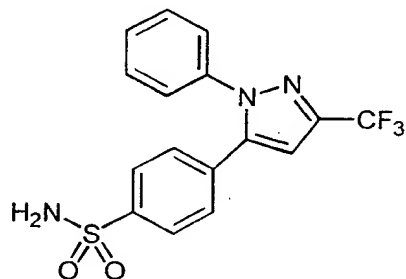
22)



4-[5-phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,

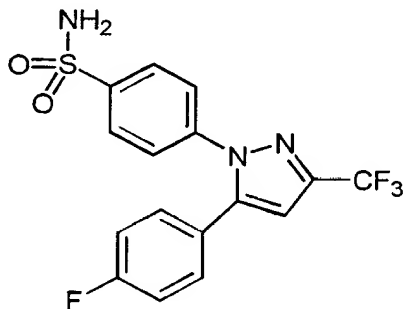
5

23)



4-[1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide,

24)

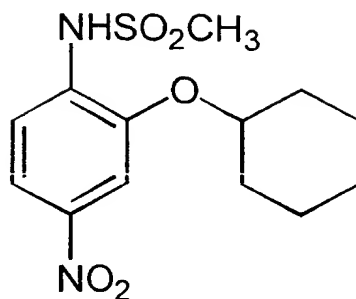


10

4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,

-298-

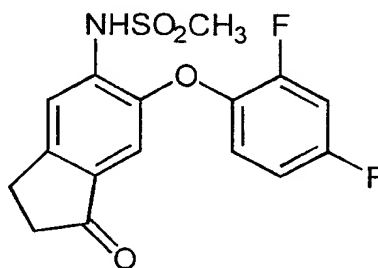
25)



N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide,

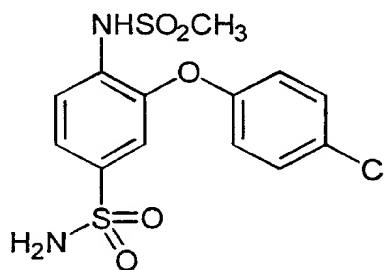
5

26)



N-[6-(2,4-difluorophenoxy)-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide,

27)

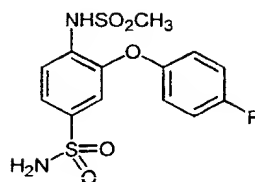


10

3-(4-chlorophenoxy)-4-[(methylsulfonyl)amino]benzenesulfonamide,

-299-

28)

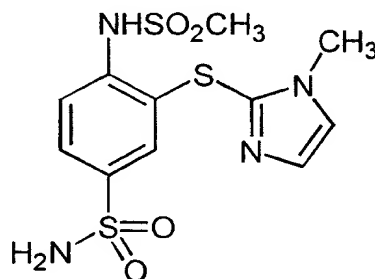


3-(4-fluorophenoxy)-4-

[(methylsulfonyl)amino]benzenesulfonamide,

5

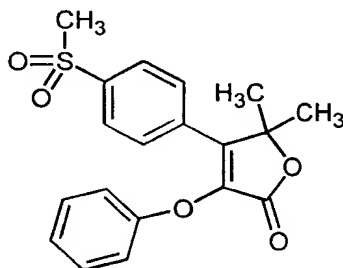
29)



3-[(1-methyl-1H-imidazol-2-yl)thio]-4

[(methylsulfonyl)amino]benzenesulfonamide,

30)

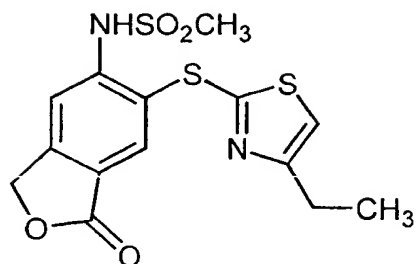


10

5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-3-
phenoxy-2(5H)-furanone,

-300-

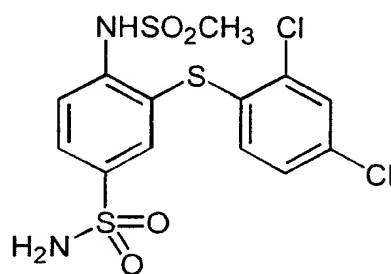
31)



N-[6-[(4-ethyl-2-thiazolyl)thio]-1,3-dihydro-1-oxo-5-isobenzofuranyl]methanesulfonamide,

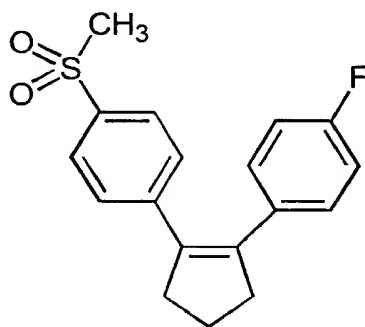
5

32)



3-[(2,4-dichlorophenyl)thio]-4-[(methanesulfonyl)amino]benzenesulfonamide,

33)

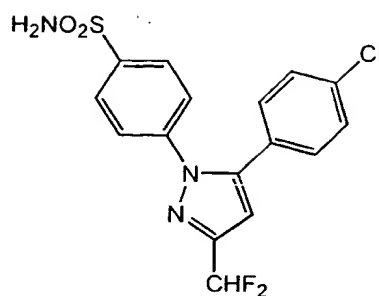


1-fluoro-4-[2-[4-(methanesulfonyl)phenyl]cyclopenten-1-yl]benzene,

10

-301-

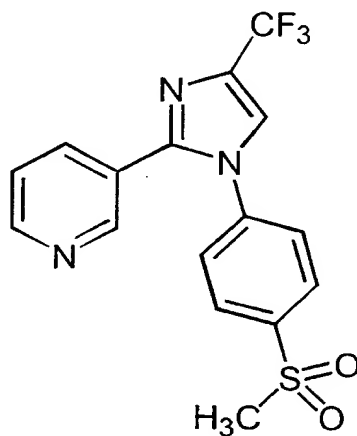
34)



4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,

5

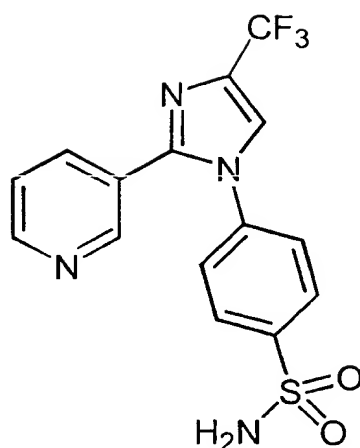
35)



3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine,

-302-

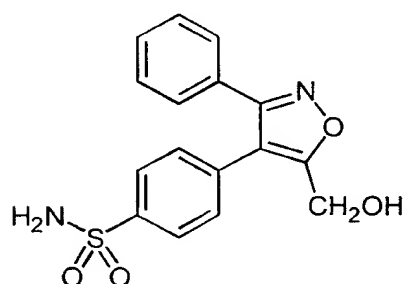
36)



4-[2-(3-pyridinyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide,

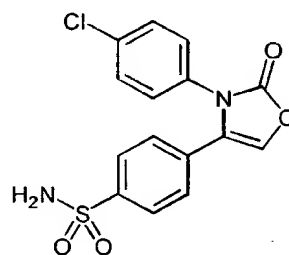
5

37)



4-[5-(hydroxymethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide,

38)

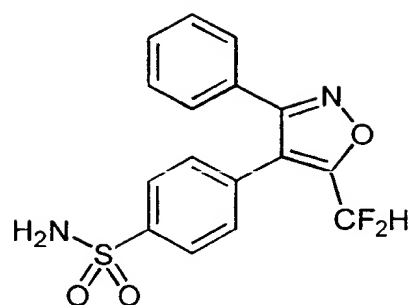


10

4-[3-(4-chlorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide,

-303-

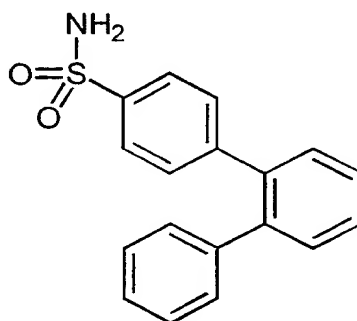
39)



4-[5-(difluoromethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide,

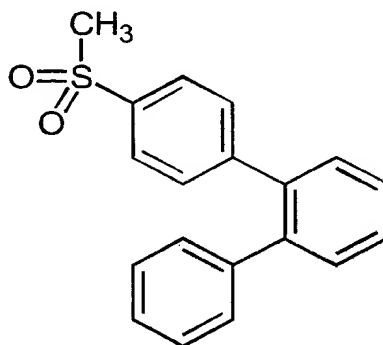
5

40)



[1,1':2',1''-terphenyl]-4-sulfonamide,

41)

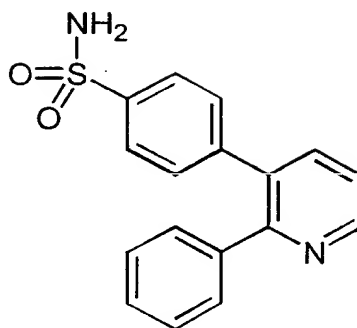


10

4-(methylsulfonyl)-1,1',2],1''-terphenyl,

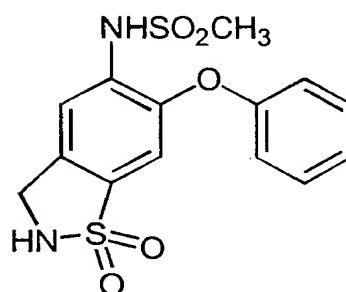
-304-

42)



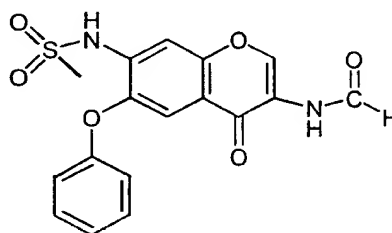
4-(2-phenyl-3-pyridinyl)benzenesulfonamide,

43)



N-(2,3-dihydro-1,1-dioxido-6-phenoxy-1,2-benzisothiazol-5-yl)methanesulfonamide, and

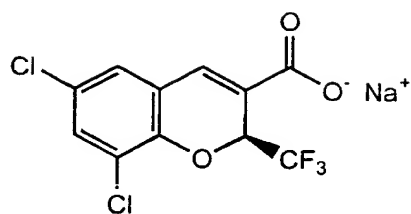
44)



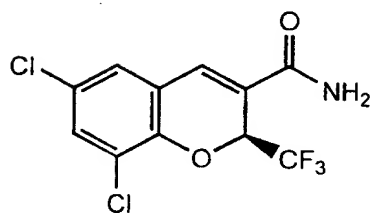
N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl]methanesulfonamide,

-305-

45)

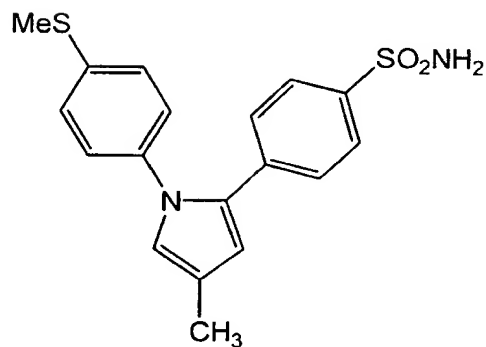


46)



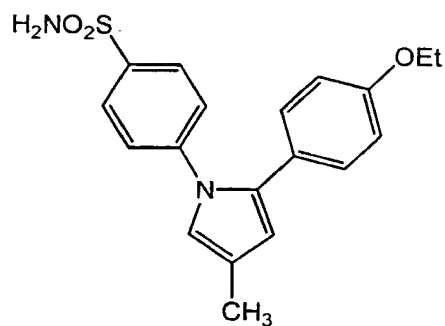
5

47)



, and

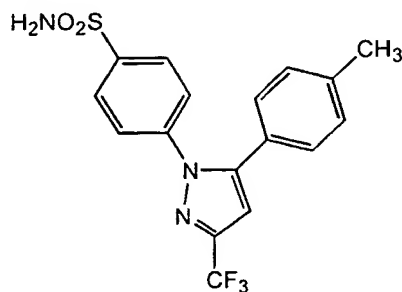
48)



114. The combination of Claim 112 wherein the
 10 cyclooxygenase-2 inhibitor is 5-chloro-3-(4-(methylsulfonyl)phenyl)-2-(methyl-5-pyridinyl)pyridine.

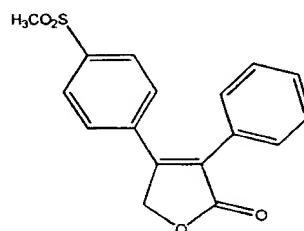
115. The combination of Claim 112 wherein the cyclooxygenase-2 inhibitor is 2-(3,5-difluorophenyl)-3-4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one.

116. The combination of Claim 112 wherein the
5 cyclooxygenase-2 inhibitor is



4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-benzenesulfonamide.

117. The combination of Claim 112 wherein the
10 cyclooxygenase-2 inhibitor is



rofecoxib, 4-(4-(methylsulfonyl)phenyl)-3-phenyl-2(5H)-furanone.

gland carcinoma, basal cell carcinoma, bronchial gland carcinomas, capillary, carcinoids, carcinoma, carcinosarcoma, cavernous, cholangiocarcinoma, chondrosarcoma, choroid plexus papilloma/carcinoma, clear

5 cell carcinoma, cystadenoma, endodermal sinus tumor, endometrial hyperplasia, endometrial stromal sarcoma, endometrioid adenocarcinoma, ependymal, epitheloid, Ewing's sarcoma, fibrolamellar, focal nodular hyperplasia, gastrinoma, germ cell tumors, glioblastoma,

10 glucagonoma, hemangioblastomas, hemangioendothelioma, hemangiomas, hepatic adenoma, hepatic adenomatosis, hepatocellular carcinoma, insulinoma, intraepithelial neoplasia, interepithelial squamous cell neoplasia, invasive squamous cell carcinoma, large cell carcinoma,

15 leiomyosarcoma, lentigo maligna melanomas, malignant melanoma, malignant mesothelial tumors, medulloblastoma, medulloepithelioma, melanoma, meningeal, mesothelial, metastatic carcinoma, mucoepidermoid carcinoma, neuroblastoma, neuroepithelial adenocarcinoma nodular

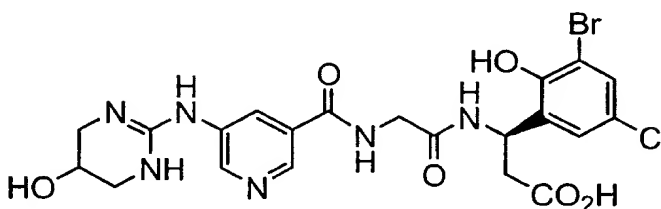
20 melanoma, oat cell carcinoma, oligodendroglial, osteosarcoma, pancreatic polypeptide, papillary serous adenocarcinoma, pineal cell, pituitary tumors, plasmacytoma, pseudosarcoma, pulmonary blastoma, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma,

25 sarcoma, serous carcinoma, small cell carcinoma, soft tissue carcinomas, somatostatin-secreting tumor, squamous carcinoma, squamous cell carcinoma, submesothelial, superficial spreading melanoma, undifferentiated carcinoma, uveal melanoma, verrucous

30 carcinoma, vipoma, well differentiated carcinoma, and Wilm's tumor.

123. The combination of Claim 112 wherein the integrin antagonist is selected from compounds, and their pharmaceutically acceptable salts thereof, of the group consisting of:

1)

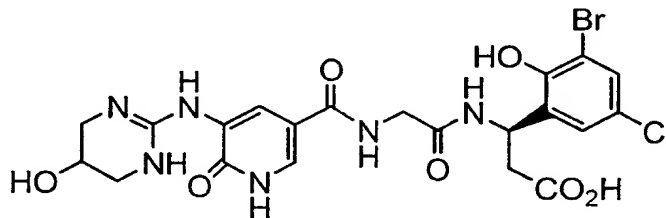


(3R)-N-[[5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]-

10

3-pyridinyl]carbonyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-L-alanine,

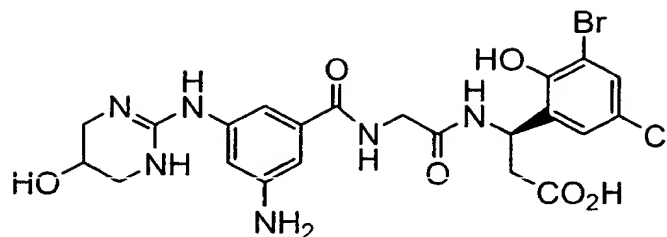
2)



15

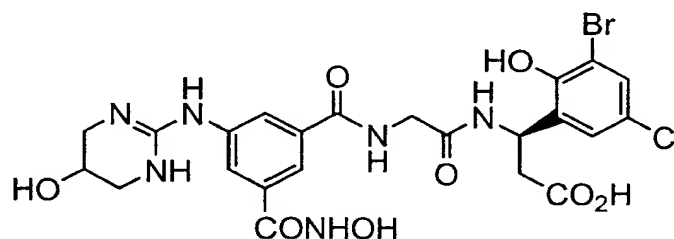
(3R)-N-[[1,6-dihydro-6-oxo-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]-3-pyridinyl]carbonyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-L-alanine,

3)



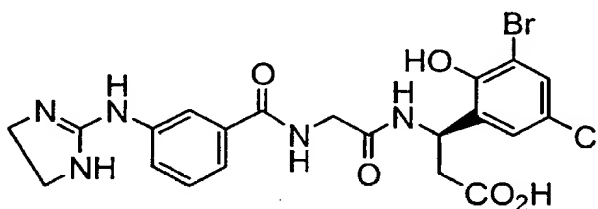
(3R)-N-[3-amino-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-L-alanine,

4)



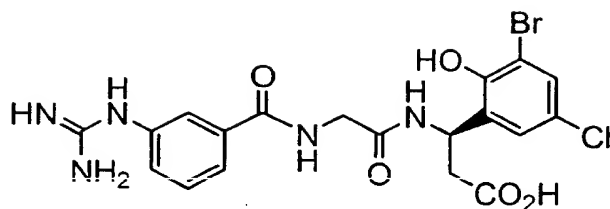
(3R)-N-[3-[(hydroxyamino)carbonyl]-5-[(1,4,5,6-tetrahydro-5-hydroxy)-2-pyrimidinyl]amino]benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-L-alanine,

5)



(3R)-N-[3-[(4,5-dihydro-1H-imidazol-2-yl)amino]benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-L-alanine,

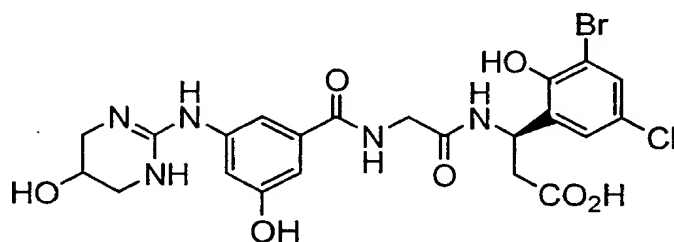
6)



(3R)-N-[3-

[(aminoiminomethyl)amino]benzoyl]glycyl-3-(3-
bromo-5-chloro-2-hydroxyphenyl)-b-alanine,

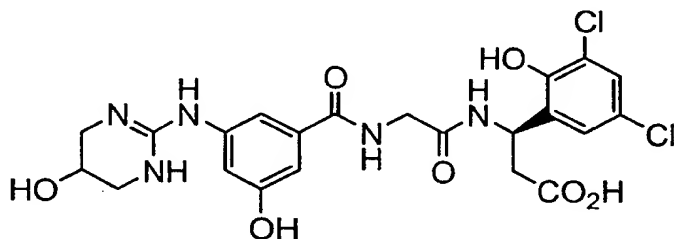
7)



(3R)-N-[3-hydroxy-5-[(1,4,5,6-tetrahydro-5-

hydroxy-2-pyrimidinyl)amino]benzoyl]glycyl-3-
(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine,

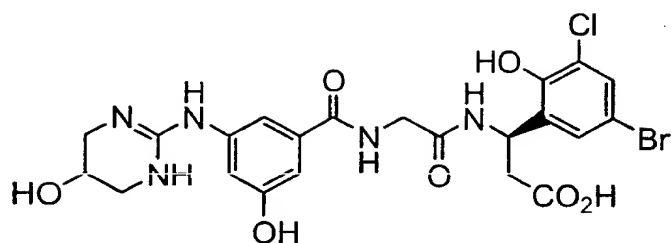
8)



(3R)-N-[3-hydroxy-5-[(1,4,5,6-tetrahydro-5-

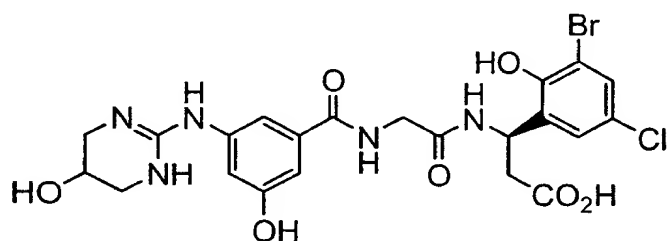
hydroxy-2-pyrimidinyl)amino]benzoyl]glycyl-3-
(3,5-dichloro-2-hydroxyphenyl)-b-alanine,

9)



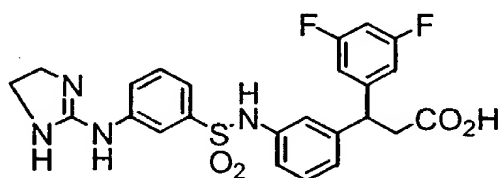
(3R)-N-[3-hydroxy-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]benzoyl]glycyl-3-(5-bromo-3-chloro-2-hydroxyphenyl)-b-alanine,

10)



(3R)-N-[3-hydroxy-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine,

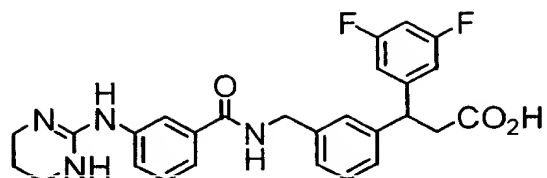
11)



b-[3-[[[3-[[4,5-dihydro-1H-imidazol-2-yl)amino]phenyl]sulfonyl]amino]phenyl]-3,5-difluorobenzenepropanoic acid,

-313-

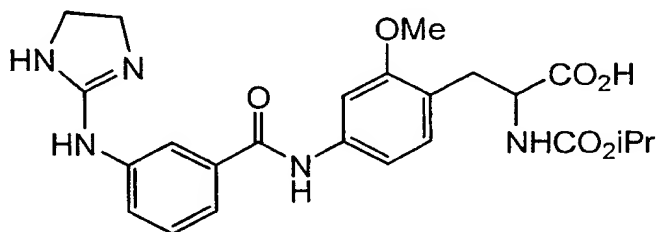
12)



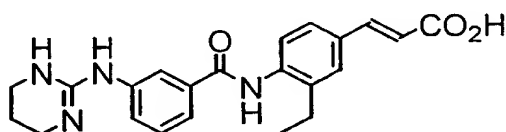
3,5-difluoro-b-[3-[[[3-[(1,4,5,6-tetrahydro-2-pyrimidinyl)amino]benzoyl]amino]methyl]phenyl] benzenepropanoic acid,

5

13)



14)

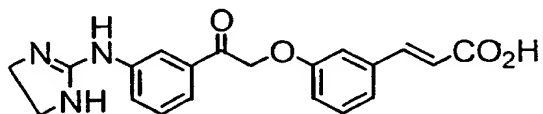


10

(2E)-3-[3-ethyl-4-[[3-[(1,4,5,6-tetrahydro-2-pyrimidinyl)amino]benzoyl]amino]phenyl]-2-propenoic acid,

15

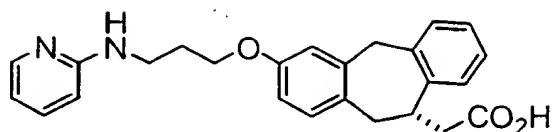
15)



(2E)-3-[3-[2-[3-[(4,5-dihydro-1H-imidazol-2-yl)amino]phenyl]-2-oxoethoxy]phenyl]-2-propenoic acid,

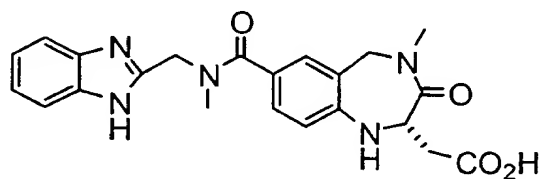
20

16)



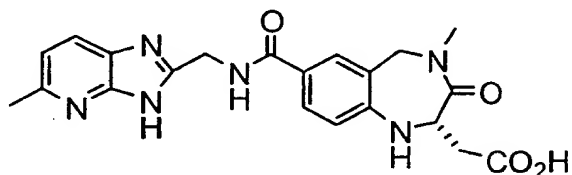
(10S)-10,11-dihydro-3-[3-(2-pyridinylamino)propoxy]-5H-dibenzo[a,d]cycloheptene-10-acetic acid,

17)



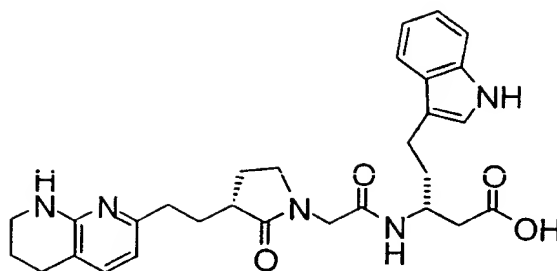
(2S)-7-[[[1H-benzimidazol-2-ylmethyl)methylamino]carbonyl]-2,3,4,5-tetrahydro-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid,

18)



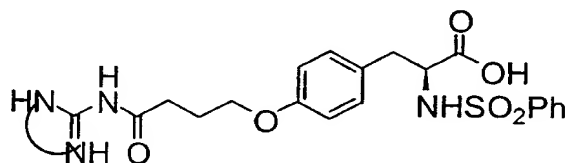
(2S)-2,3,4,5-tetrahydro-4-methyl-7-[[[(5-methyl-1H-imidazo[4,5-b]pyridin-2-yl)methyl]amino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid,

19)



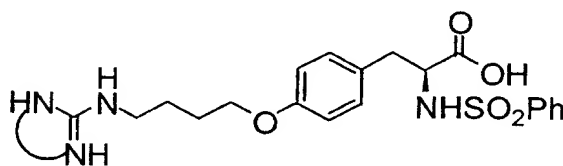
(bR) -b-[[[(3R)-2-oxo-3-[2-(1,5,6,7-tetrahydro-1,8-naphthyridin-2-yl)ethyl]-1-pyrrolidinyl]acetyl]amino]-1H-indole-3-pentanoic acid,

20)

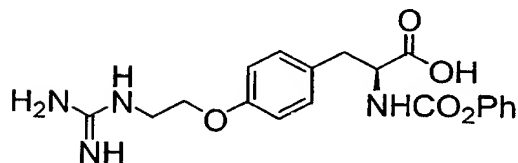


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21)

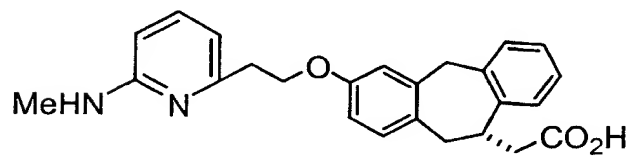


22)



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23)

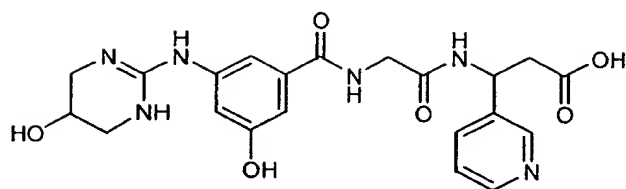


24) Vitaxin antibody(Ixsys),

25) Merck KGaA EMD-121974, cyclo[RGDf-N(Me)V-],

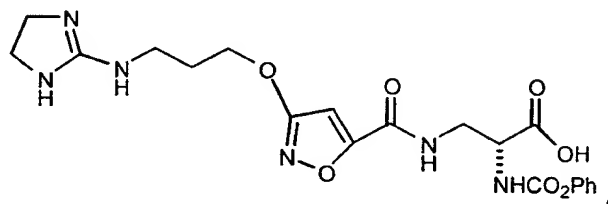
5

26)

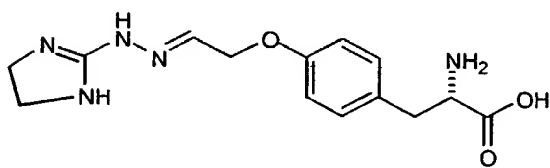


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27)



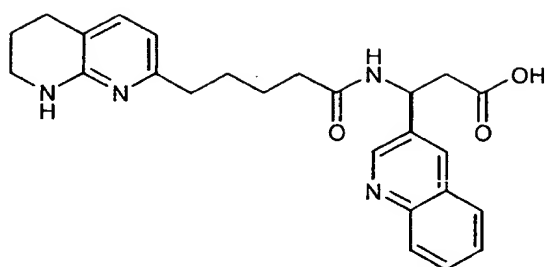
28)



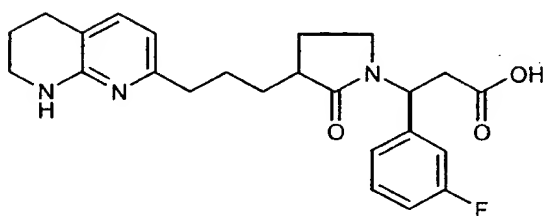
15

-317-

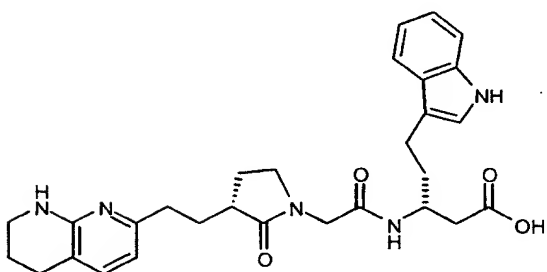
29)



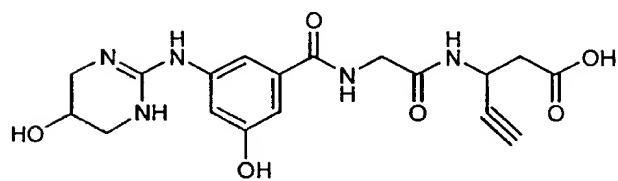
30)



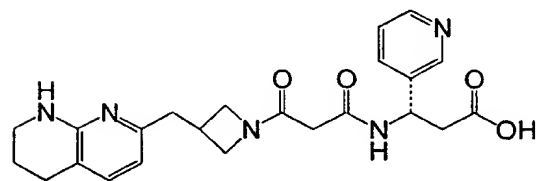
31)



32)

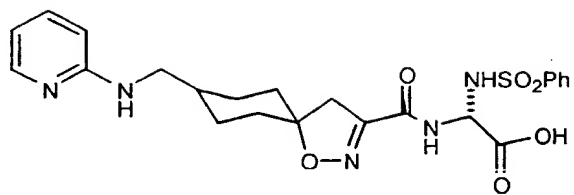


33)



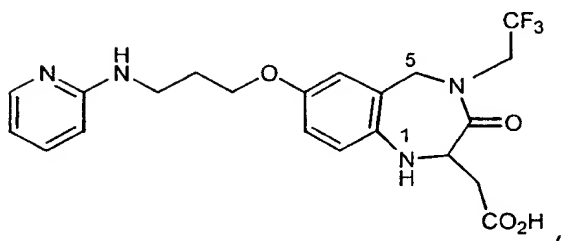
-318-

34)

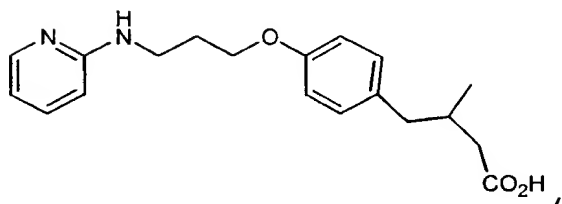


35)

5

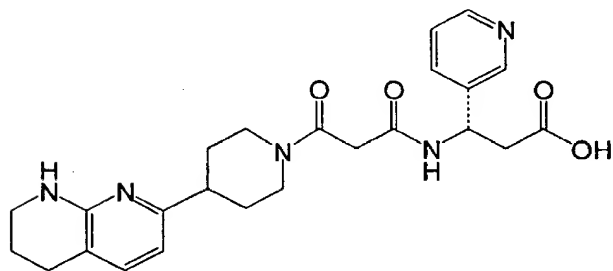


36)

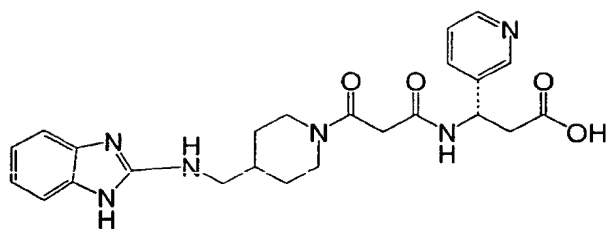


10

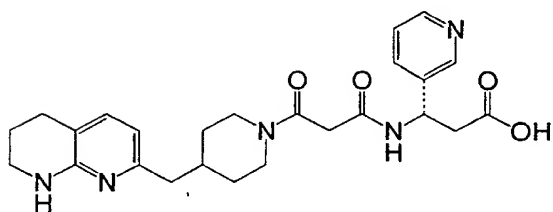
37)



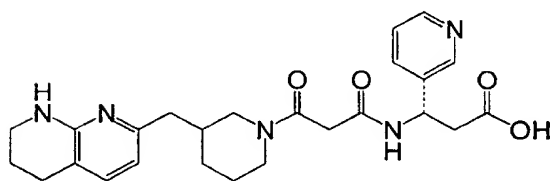
38)



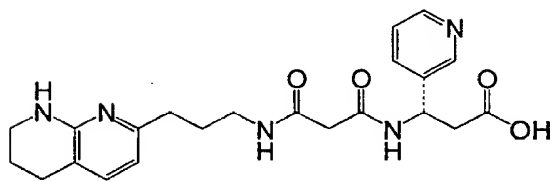
39)



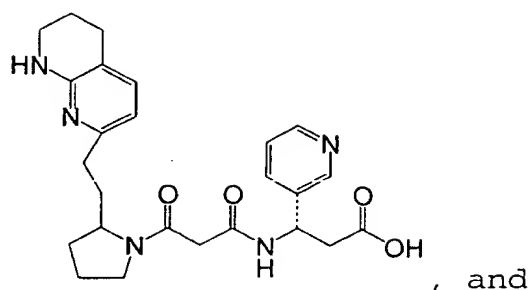
40)



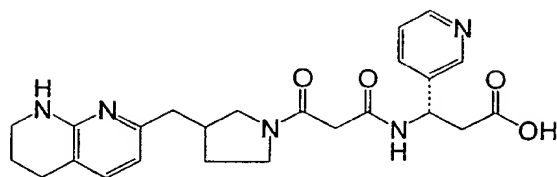
41)



42)

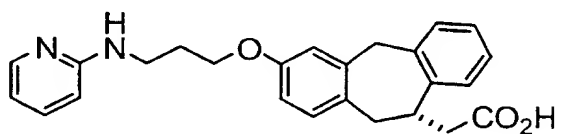


43)



5

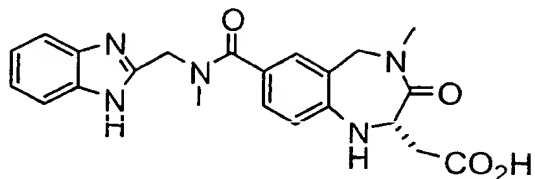
124. The combination of Claim 112 wherein the integrin antagonist is



10

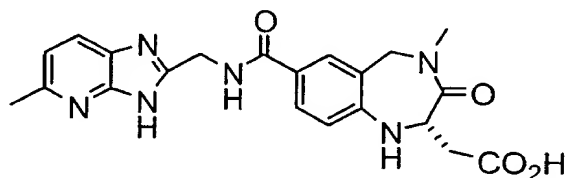
(10S)-10,11-dihydro-3-[3-(2-pyridinylamino)propoxy]-5H-dibenzo[a,d]cycloheptene-10-acetic acid.

125. The combination of Claim 112 wherein the integrin antagonist is



5 (2S)-7-[[[(1H-benzimidazol-2-ylmethyl)methylamino]carbonyl]-2,3,4,5-tetrahydro-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid.

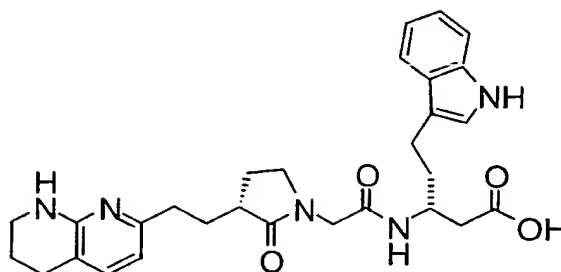
126. The combination of Claim 112 wherein the integrin antagonist is



10 (2S)-2,3,4,5-tetrahydro-4-methyl-7-[[[(5-methyl-1H-imidazo[4,5-b]pyridin-2-yl)methyl]amino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid.

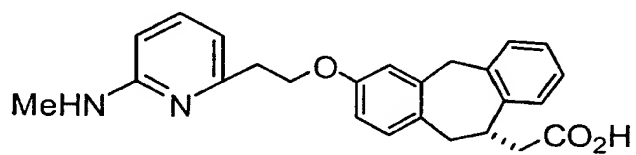
-322-

127. The combination of Claim 112 wherein the integrin antagonist is



5 (bR)-b-[[[(3R)-2-oxo-3-[2-(1,5,6,7-tetrahydro-1,8-naphthyridin-2-yl)ethyl]-1-pyrrolidinyl]acetyl]amino]-1H-indole-3-pentanoic acid.

128. The combination of Claim 112 wherein the
10 integrin antagonist is



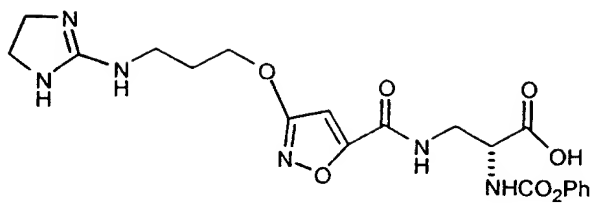
129. The combination of Claim 112 wherein the
15 integrin antagonist is Vitaxin antibody(Ixsys).

130. The combination of Claim 112 wherein the integrin antagonist is Merck KGaA EMD-121974, cyclo[RGDf-N(Me)V-]

20

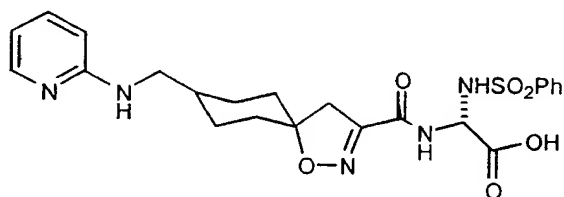
131. The combination of Claim 112 wherein the integrin antagonist is

-323-



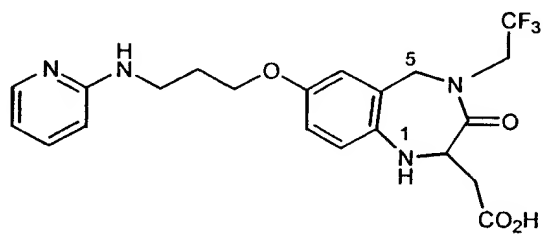
132. The combination of Claim 112 wherein the integrin antagonist is

5

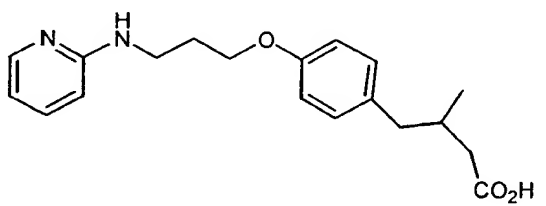


133. The combination of Claim 112 wherein the integrin antagonist is

10



134. The combination of Claim 112 wherein the integrin antagonist is



15

-324-

135. The method of Claim 1 wherein the antineoplastic agent is anastrozole.

136. The method of Claim 1 wherein the
5 antineoplastic agent is calcium carbonate.

137. The method of claim 1 wherein the antineoplastic agent is exemestane.

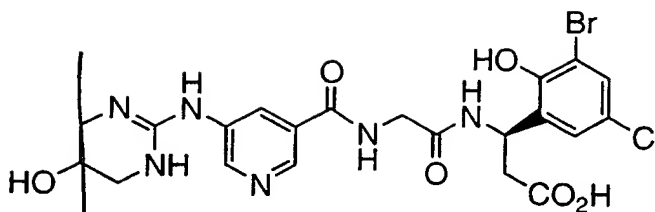
10 138. The method of Claim 56 wherein the antineoplastic agent is anastrozole.

139. The method of Claim 56 wherein the antineoplastic agent is calcium carbonate.

15 140. The method of claim 56 wherein the antineoplastic agent is exemestane.

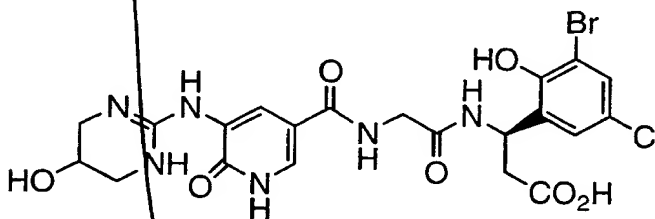
20 141. A method for treating or preventing a neoplasia disorder in a mammal in need of such treatment or prevention, which method comprises administering to said mammal a therapeutically-effective amount of a combination of a cyclooxygenase-2 inhibitor and an integrin antagonist, wherein said integrin antagonist is
25 selected from compounds, and their pharmaceutically acceptable salts thereof, of the group consisting of:

1)



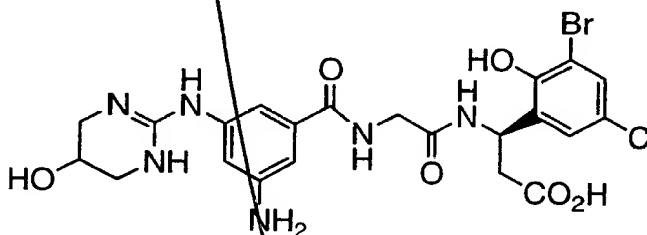
(3R)-N-[[5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]-3-pyridinyl]carbonyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine,

2)



(3R)-N-[[1,6-dihydro-6-oxo-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]-3-pyridinyl]carbonyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine,

3)

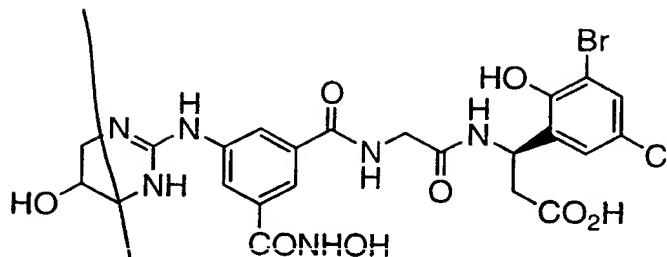


(3R)-N-[3-amino-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine,

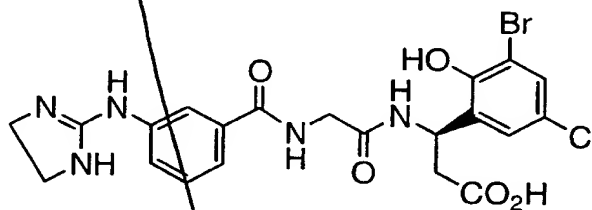
4)

See Cont

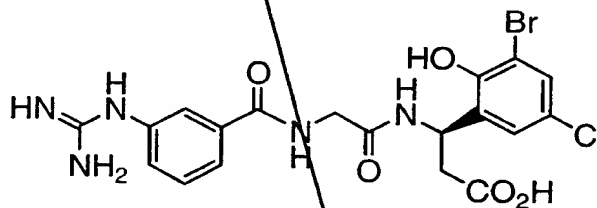
-326-



(3R)-N-[3-[(hydroxyamino)carbonyl]-5-
[(1,4,5,6-tetrahydro-5-hydroxy)-2-
pyrimidinyl]amino]benzoyl]glycyl-3-(3-bromo-5-
chloro-2-hydroxyphenyl)-b-alanine,

5)
5

(3R)-N-[3-[(4,5-dihydro-1H-imidazol-2-
yl)amino]benzoyl]glycyl-3-(3-bromo-5-chloro-2-
hydroxyphenyl)-b-alanine,

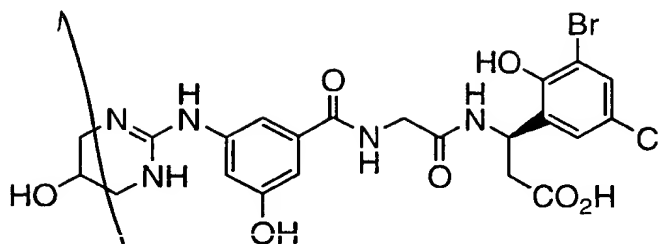
6)
10

(3R)-N-[3-
[(aminoiminomethyl)amino]benzoyl]glycyl-3-(3-
bromo-5-chloro-2-hydroxyphenyl)-b-alanine,

7)
15

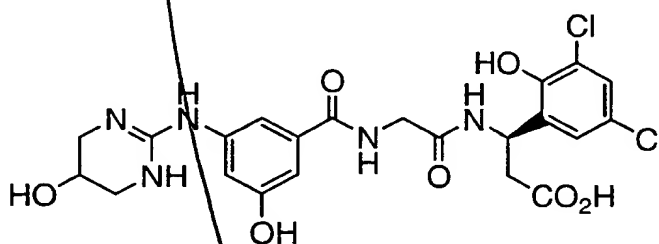
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-327-



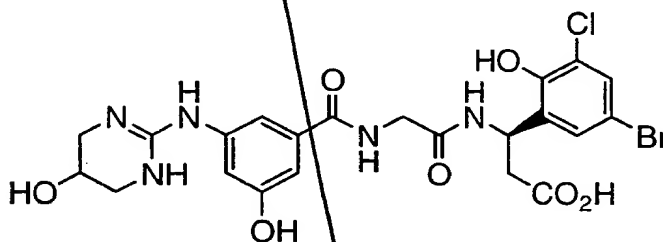
(3R)-N-[3-hydroxy-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine,

8)



(3R)-N-[3-hydroxy-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]benzoyl]glycyl-3-(3,5-dichloro-2-hydroxyphenyl)-b-alanine,

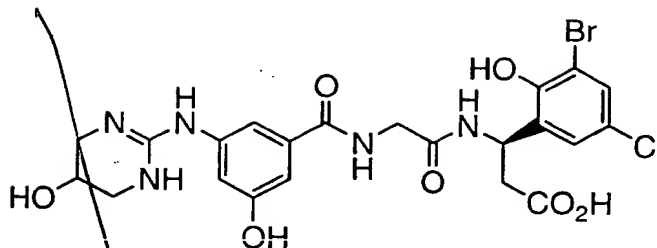
9)



(3R)-N-[3-hydroxy-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]benzoyl]glycyl-3-(5-bromo-3-chloro-2-hydroxyphenyl)-b-alanine,

10)

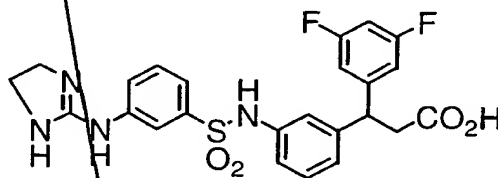
-328-



(3R)-N-[3-hydroxy-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine,

5

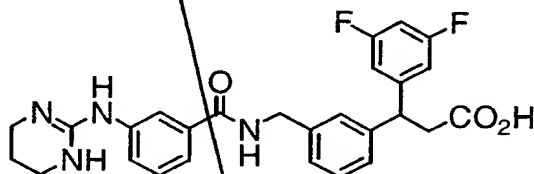
11)



b-[3-[[[3-[[4,5-dihydro-1H-imidazol-2-yl)amino]phenyl]sulfonyl]amino]phenyl]-3,5-difluorobenzenepropanoic acid,

10

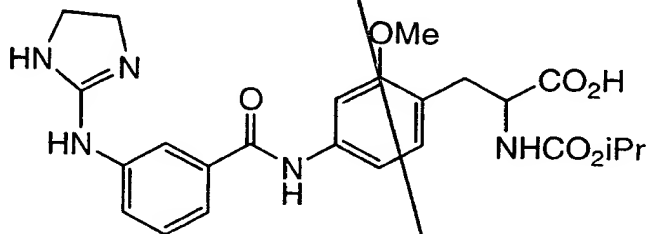
12)



3,5-difluoro-b-[3-[[[3-[(1,4,5,6-tetrahydro-2-pyrimidinyl)amino]benzoyl]amino]methyl]phenyl]benzenepropanoic acid,

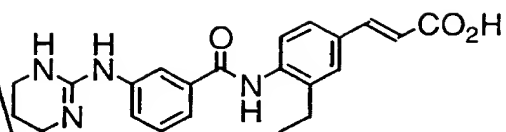
15

13)



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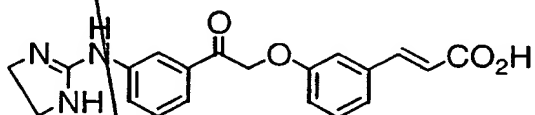
14)



(2E)-3-[3-ethyl-4-[[3-[(1,4,5,6-tetrahydro-2-pyrimidinyl)amino]benzoyl]amino]phenyl]-2-propenoic acid,

5

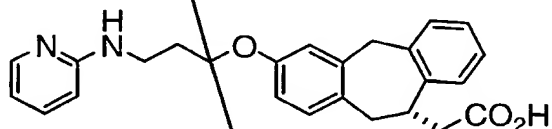
15)



(2E)-3-[3-[2-[3-[(4,5-dihydro-1H-imidazol-2-yl)amino]phenyl]-2-oxoethoxy]phenyl]-2-propenoic acid,

10

16)

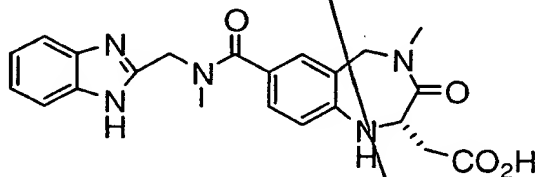


(10S)-10,11-dihydro-3-[3-(2-pyridinylamino)propoxy]-5H-dibenzo[a,d]cycloheptene-10-acetic acid,

15

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17)

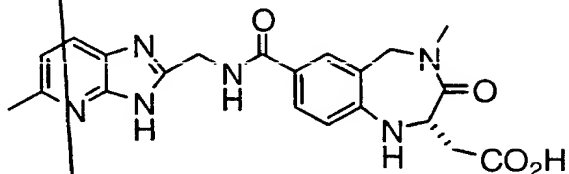


(2S)-7-[[[(1H-benzimidazol-2-ylmethyl)methylamino]carbonyl]-2,3,4,5-tetramethyl-2,3,4,5-tetrahydro-1H-benzimidazol-2-yl]-2-propenoic acid,

-330-

tetrahydro-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid,

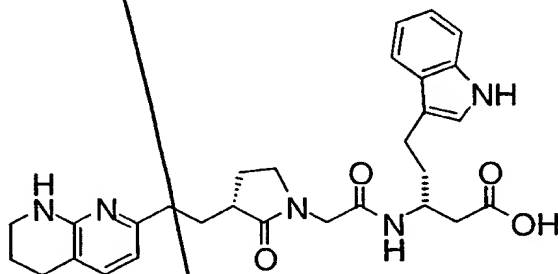
18)



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(2S)-2,3,4,5-tetrahydro-4-methyl-7-[[[(5-methyl-1H-imidazo[4,5-b]pyridin-2-yl)methyl]amino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid,

19)

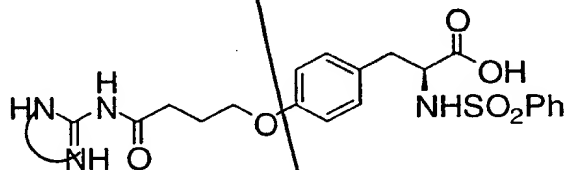


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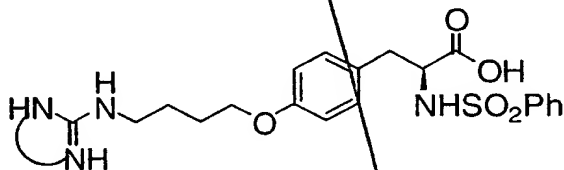
(bR)-b-[[[(3R)-2-oxo-3-[2-(1,5,6,7-tetrahydro-1,8-naphthyridin-2-yl)ethyl]-1-pyrrolidinyl]acetyl]amino]-1H-indole-3-pentanoic acid,

15

20)



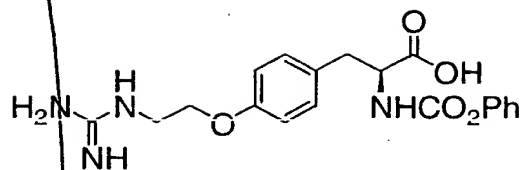
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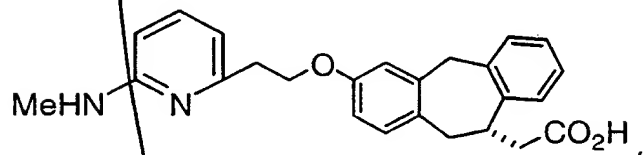
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-331-

22)



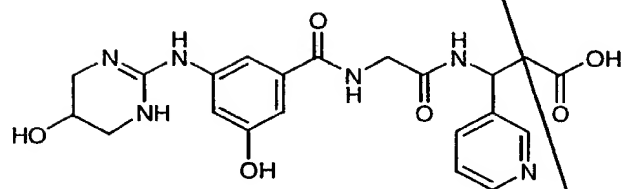
23)



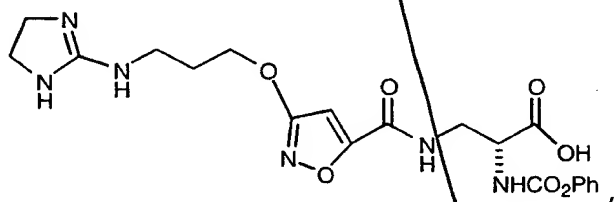
24) Vitaxin antibody(Ixsys),

25) Merck KGaA EMD-121974, cyclo[RGDf-N(Me)V-],

26)

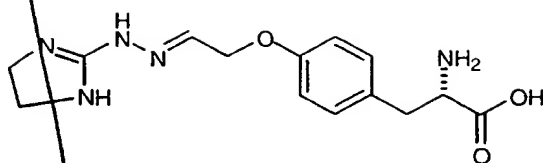


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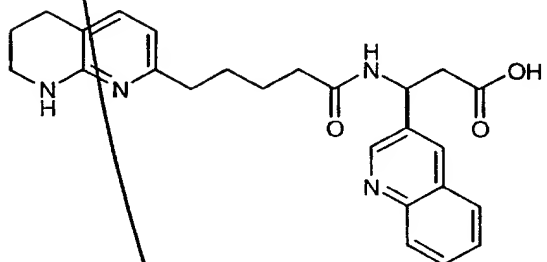


-332-

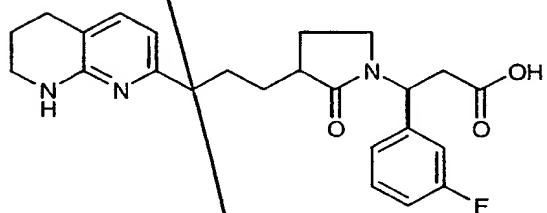
28)



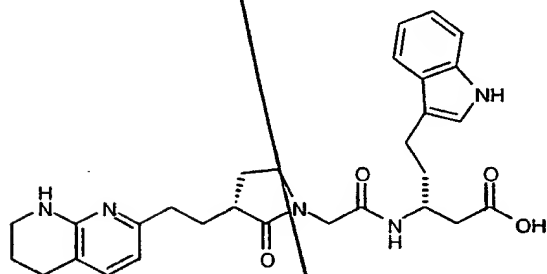
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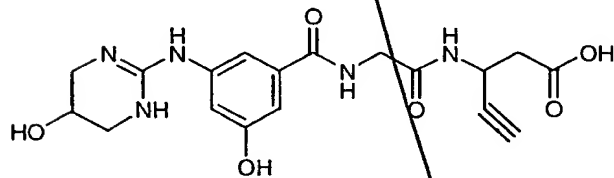
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31)



32)



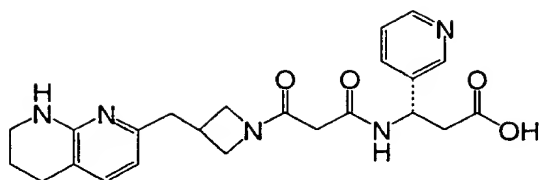
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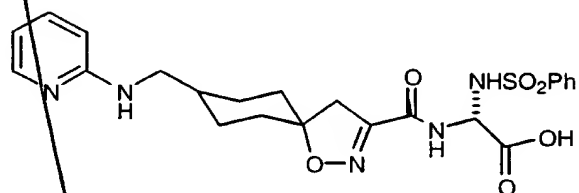
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- 333 -

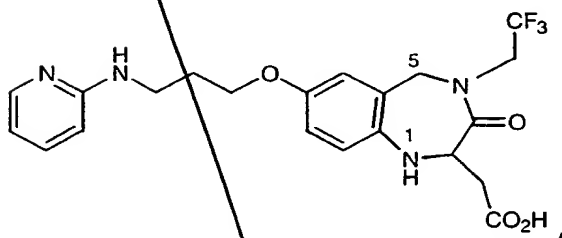
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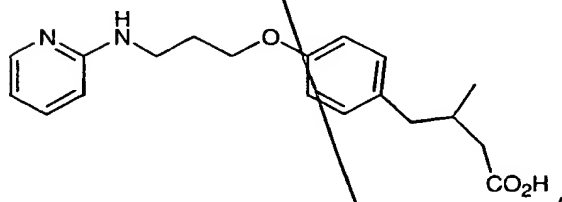
34)



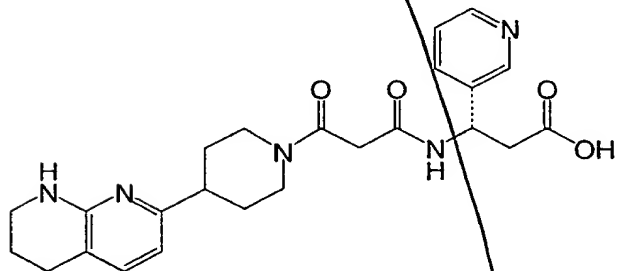
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36)



37)



38)

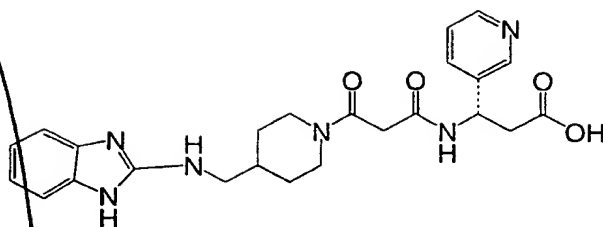
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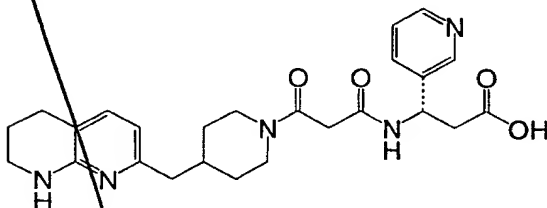
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-334-

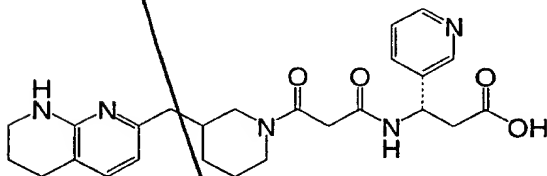
39)



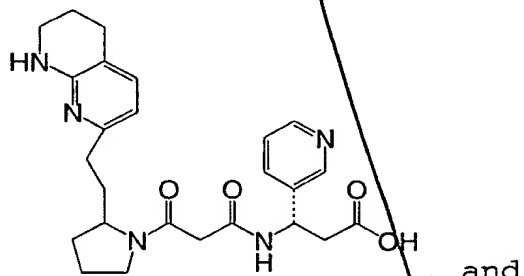
40)



41)



42)



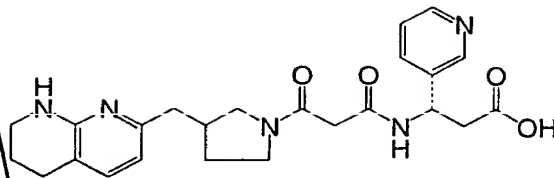
, and

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43)



5 142. The method of Claim 141 comprising
administering to said mammal a therapeutically-effective
amount of a combination of an cyclooxygenase-2
inhibitor, an integrin antagonist, and an antineoplastic
agent, wherein the antineoplastic agent is selected from
10 the group consisting of anastrozole, calcium carbonate,
capecitabine, carboplatin, cisplatin, Cell Pathways CP-
461, docetaxel, doxorubicin, etoposide, fluorouracil (5-
FU), fluoxymestrine, gemcitabine, goserelin, irinotecan,
ketoconazole, letrozol, leucovorin, levamisole,
15 megestrol, mitoxantrone, paclitaxel, raloxifene,
retinoic acid, tamoxifen, thiotepa, topotecan,
toremifene, vinorelbine, vinblastine, vincristine,
selenium (selenomethionine), ursodeoxycholic acid,
sulindac sulfone and eflornithine (DFMO).

20

 143. The method of Claim 141 comprising
administering to said mammal a therapeutically-effective
amount of a combination of radiation, a cyclooxygenase-2
inhibitor and an integrin antagonist.

25

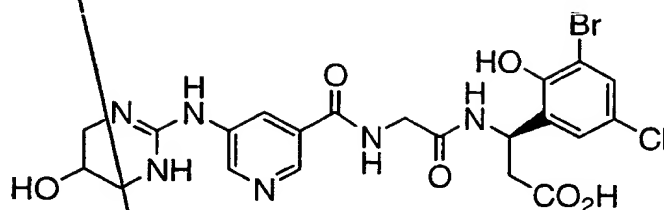
 144. A combination comprising a cyclooxygenase-2
inhibitor and an integrin antagonist, wherein said
integrin antagonist is selected from compounds, and

Sub A!
Cont

-336-

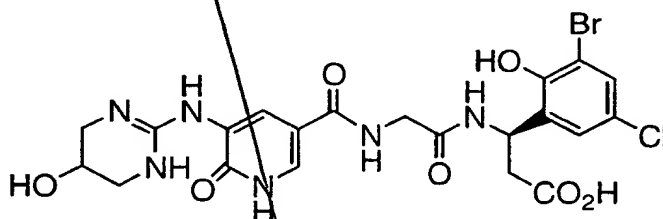
their pharmaceutically acceptable salts thereof, of the group consisting of:

1)



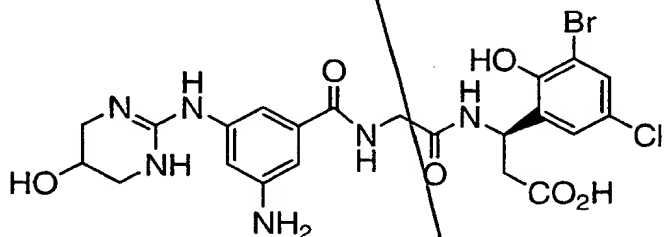
(3R)-N-[[5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]-3-pyridinyl]carbonyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine,

2)



(3R)-N-[[1,6-dihydro-6-oxo-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]-3-pyridinyl]carbonyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine,

3)



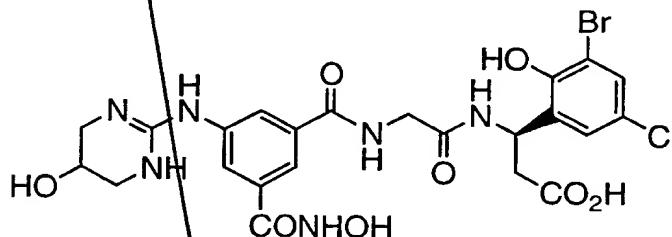
Sub 1
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-337-

(3R)-N-[3-amino-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine,

5

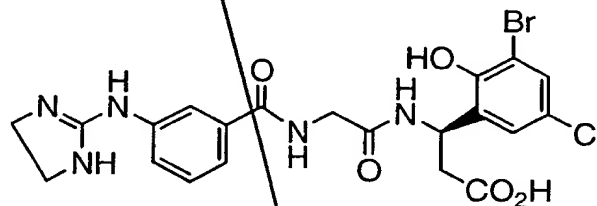
4)



(3R)-N-[3-[(hydroxyamino)carbonyl]-5-[(1,4,5,6-tetrahydro-5-hydroxy)-2-pyrimidinyl)amino]benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine,

10

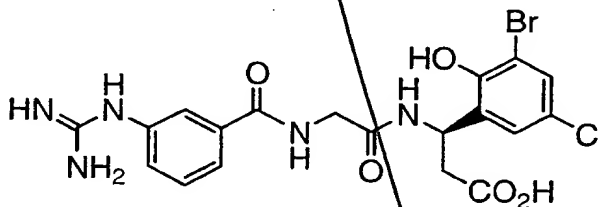
5)



(3R)-N-[3-[(4-,5-dihydro-1H-imidazol-2-yl)amino]benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine,

15

6)



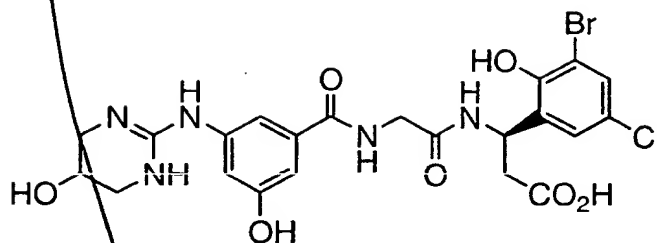
(3R)-N-[3-[(aminoiminomethyl)amino]benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine,

20

Sub B
Cont

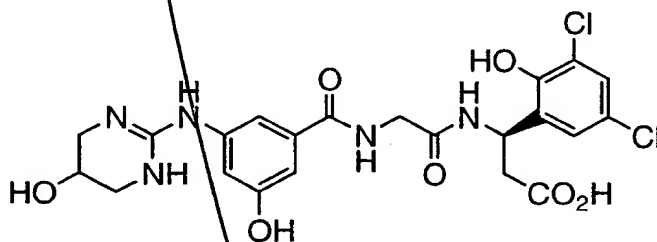
-338-

7)



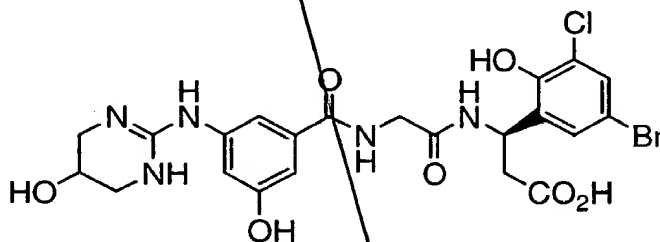
(3R)-N-[3-hydroxy-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine,

8)



(3R)-N-[3-hydroxy-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]benzoyl]glycyl-3-(3,5-dichloro-2-hydroxyphenyl)-b-alanine,

9)

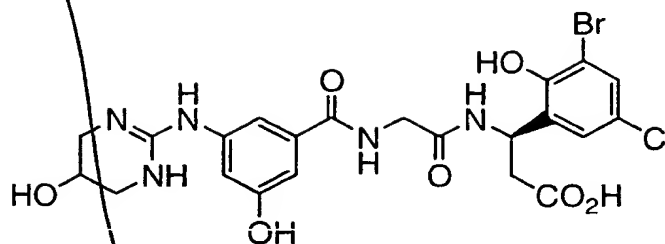


(3R)-N-[3-hydroxy-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]benzoyl]glycyl-3-(5-bromo-3-chloro-2-hydroxyphenyl)-b-alanine,

10)

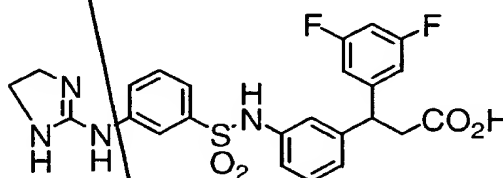
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-339-



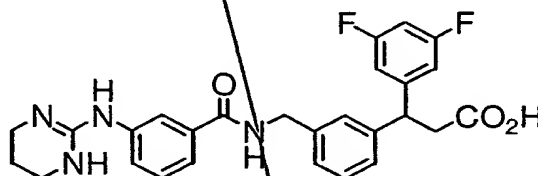
(3R)-N-[3-hydroxy-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine,

5 11)



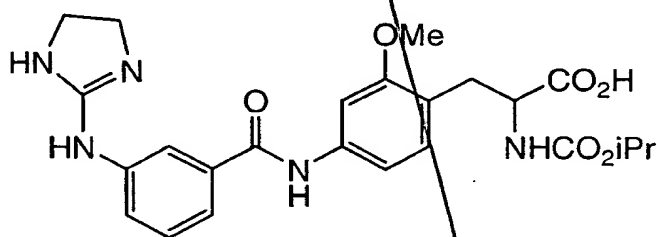
b-[3-[[[3-[[4,5-dihydro-1H-imidazol-2-yl)amino]phenyl]sulfonyl]amino]phenyl]-3,5-difluorobenzenepropanoic acid,

10 12)



3,5-difluoro-b-[3-[[[3-[(1,4,5,6-tetrahydro-2-pyrimidinyl)amino]benzoyl]amino]methyl]phenyl]benzenepropanoic acid,

15 13)

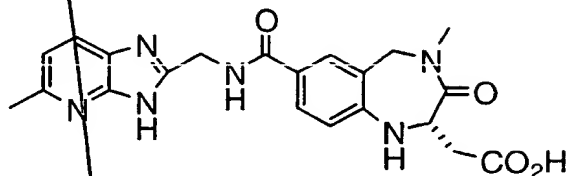


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-341-

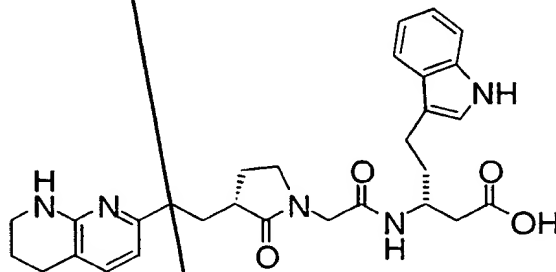
tetrahydro-4-methyl-3-oxo-1H-1,4-
benzodiazepine-2-acetic acid,

18)



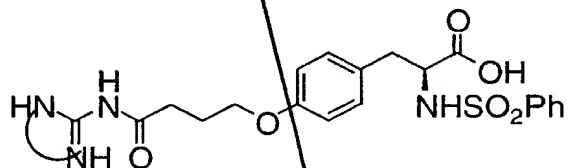
(2S)-2,3,4,5-tetrahydro-4-methyl-7-[[[(5-
methyl-1H-imidazo[4,5-b]pyridin-2-
yl)methyl]amino]carbonyl]-3-oxo-1H-1,4-
benzodiazepine-2-acetic acid,

19)

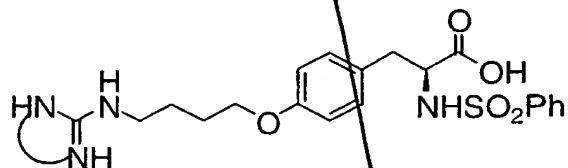


(bR)-b-[[[(3R)-2-oxo-3-[2-(1,5,6,7-tetrahydro-
1,8-naphthyridin-2-yl)ethyl]-1-
pyrrolidinyl]acetyl]amino]-1H-indole-3-
pentanoic acid,

20)

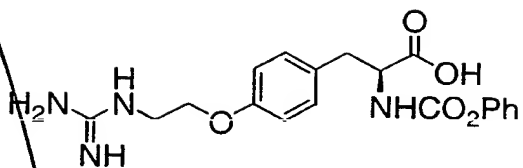


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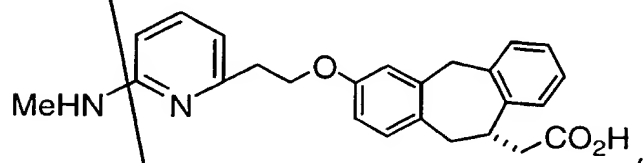


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22)



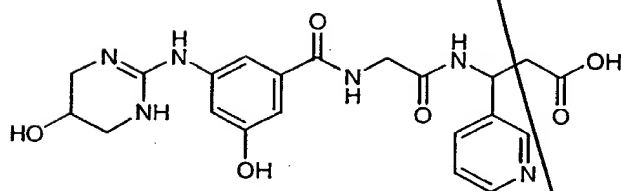
23)



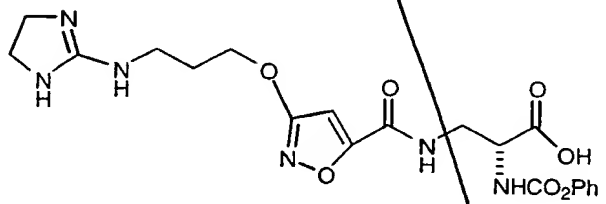
24) Vitaxin antibody (Ixsys),

25) Merck KGaA EMD-121974, cyclo[RGDf-N(Me)V-],

26)



27)



5

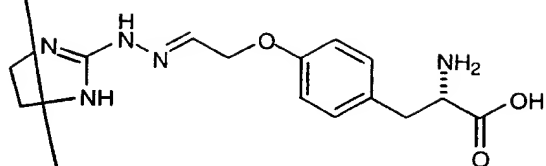
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15

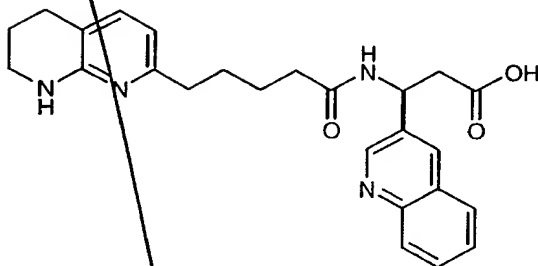
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-343-

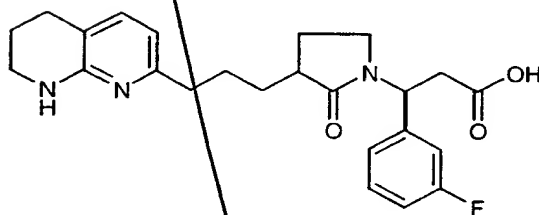
28)



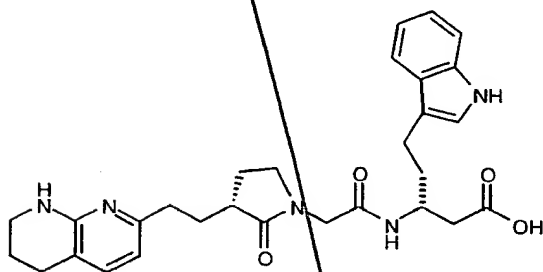
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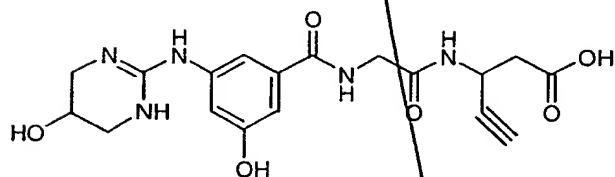
30)



31)



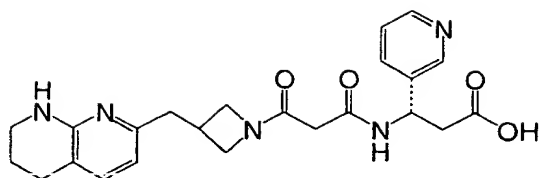
32)



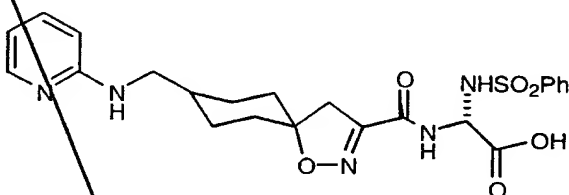
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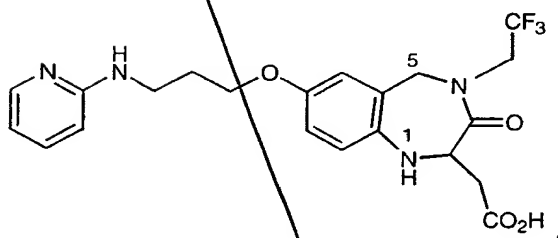
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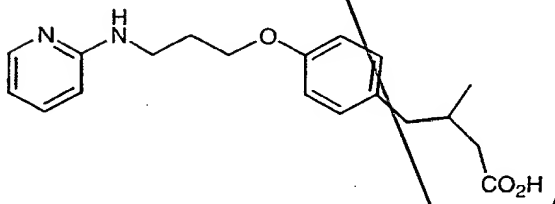
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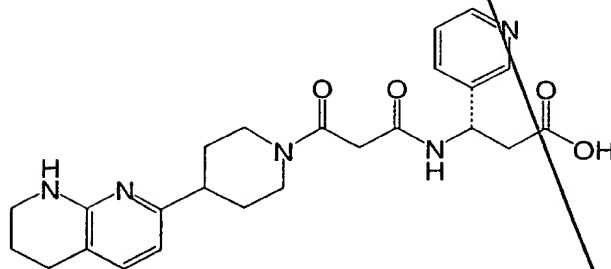
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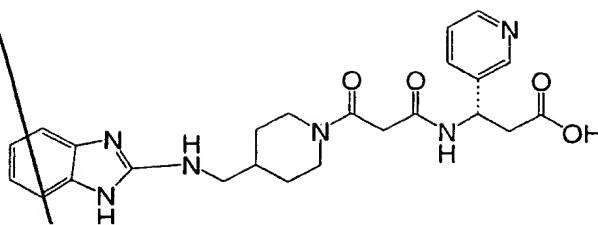
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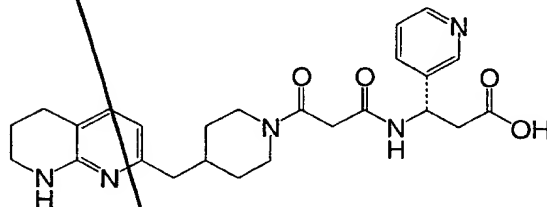
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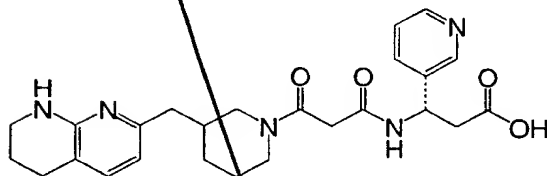
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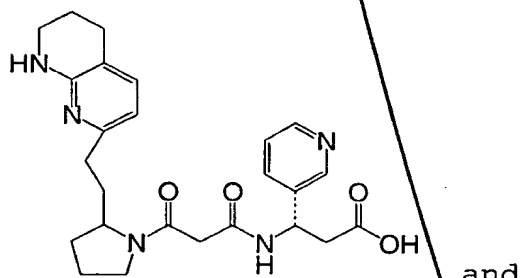
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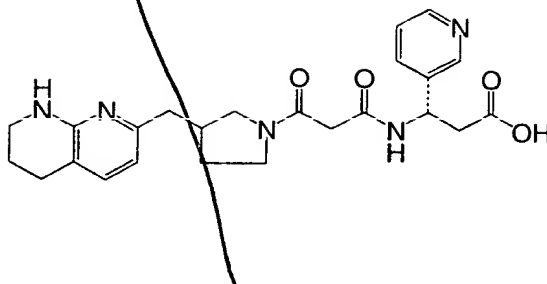
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